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Weber et al.

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(54) **METHOD FOR SPRAY-COATING A MEDICAL DEVICE HAVING TUBULAR WALL SUCH AS A STENT**

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Related U.S. Application Data

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(51) **Int. Cl.**

A61L 27/00	(2006.01)
A61L 27/28	(2006.01)
A61L 29/00	(2006.01)
B05D 1/02	(2006.01)
B05D 7/22	(2006.01)

(52) **U.S. Cl.** **427/2.24**; 427/457; 427/458; 427/469; 427/476; 427/2.1; 427/485; 427/427.4

(58) **Field of Classification Search** 427/457, 427/458, 469, 475–476, 483, 485, 421.1, 427/427.4

See application file for complete search history.

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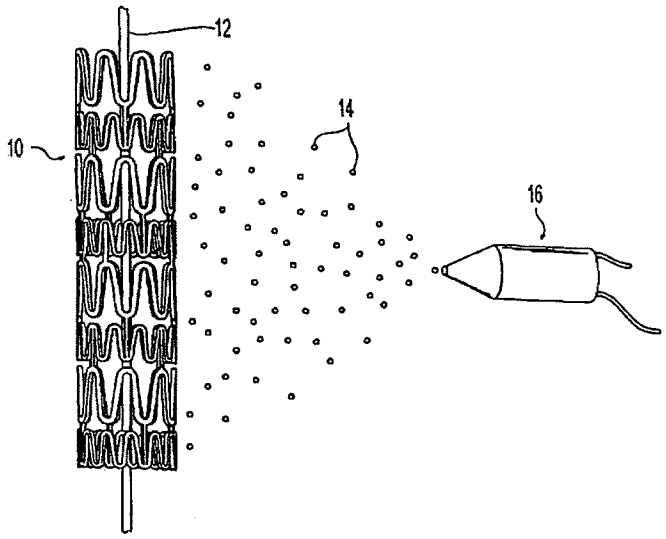
(57) **ABSTRACT**

A method for electrostatic spray-coating a medical device having a tubular wall, such as a stent, having an inner surface, an outer surface and openings therein. The tubular wall is grounded or electrically charged, and an electrically charged conductive core wire is located axially through the center of the stent. An electrical potential is applied to the conductive core wire to impart an electrical charge to the conductive core wire. The tubular wall is exposed to an electrically charged coating formulation, and the electrically charged coating formulation is deposited onto a portion of the tubular wall to form a coating. The electrical potentials of the conductive core wire and tubular wall can be repeatedly alternated.

28 Claims, 4 Drawing Sheets



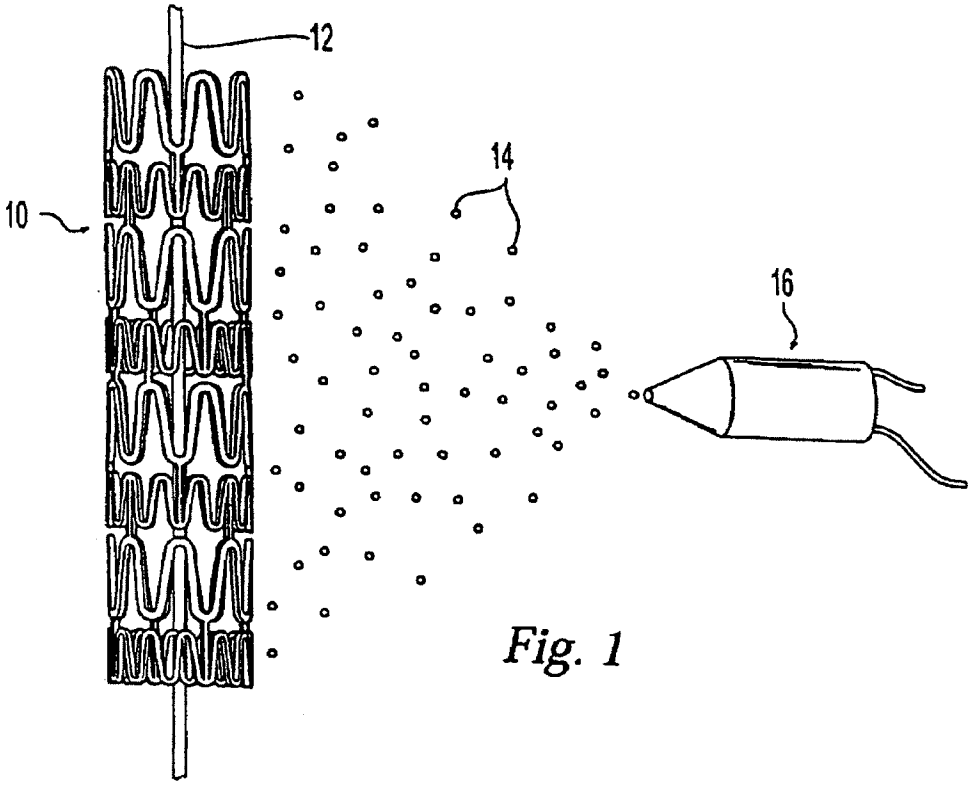


Fig. 1

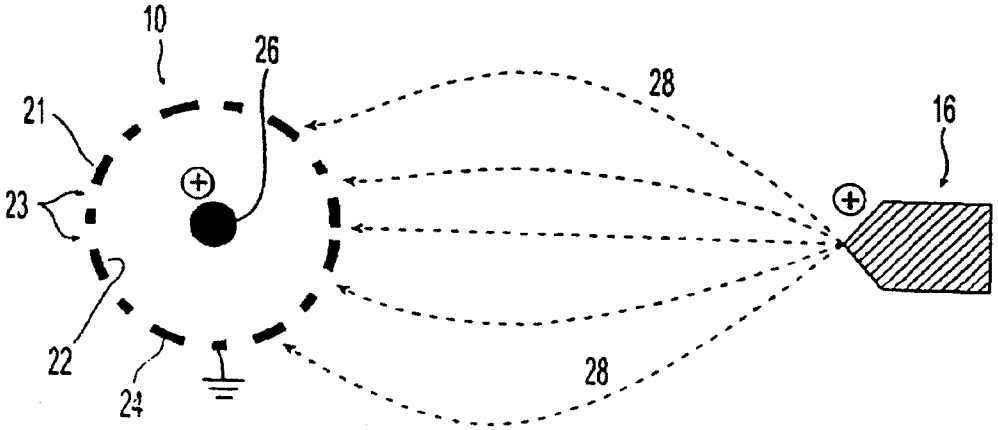


Fig. 2

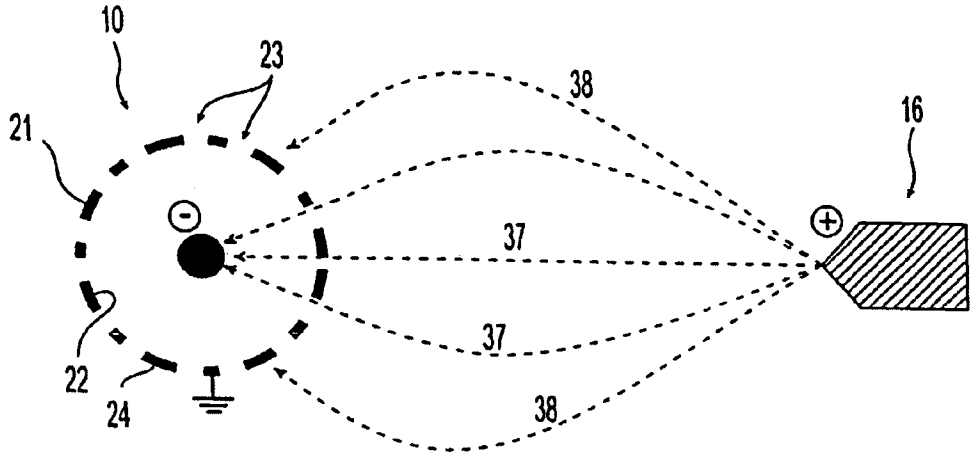


Fig. 3

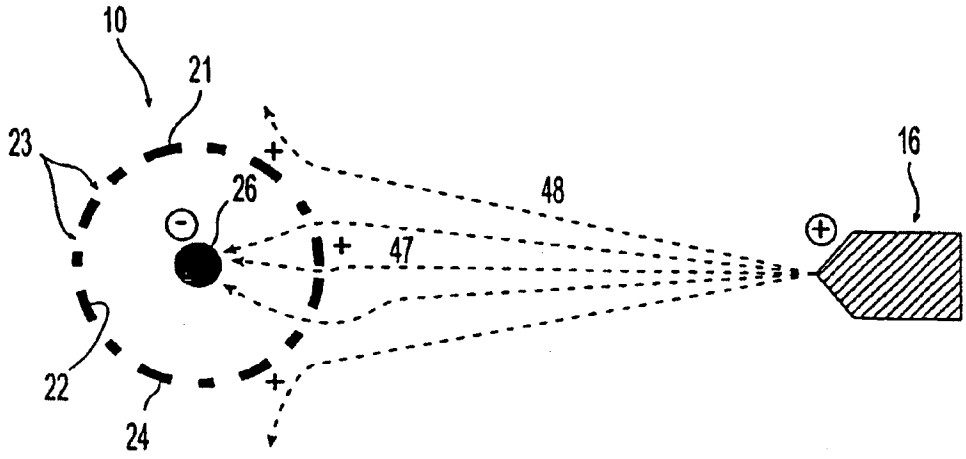


Fig. 4

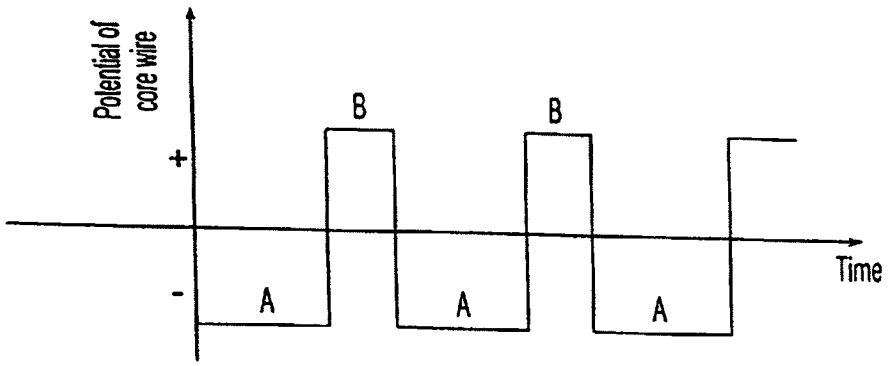


Fig. 5

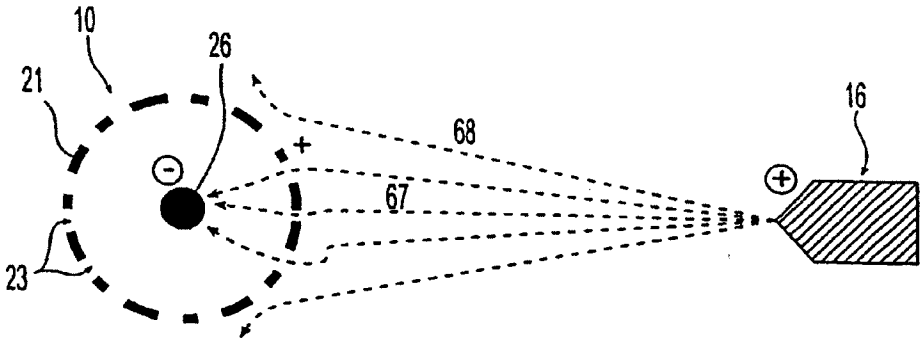


Fig. 6A

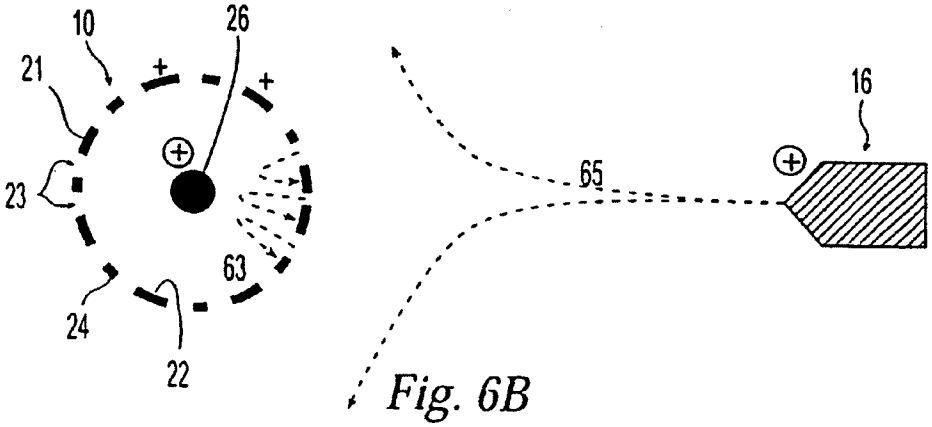


Fig. 6B

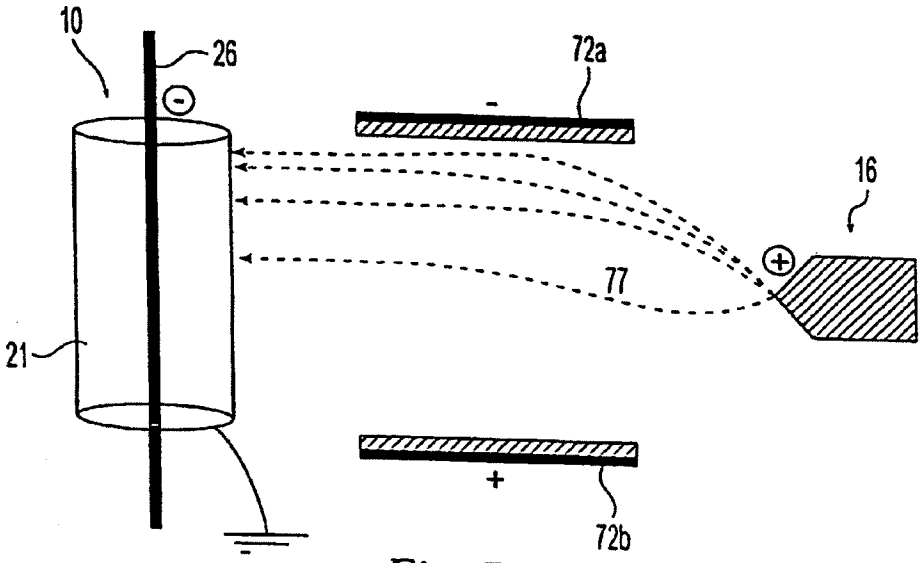


Fig. 7

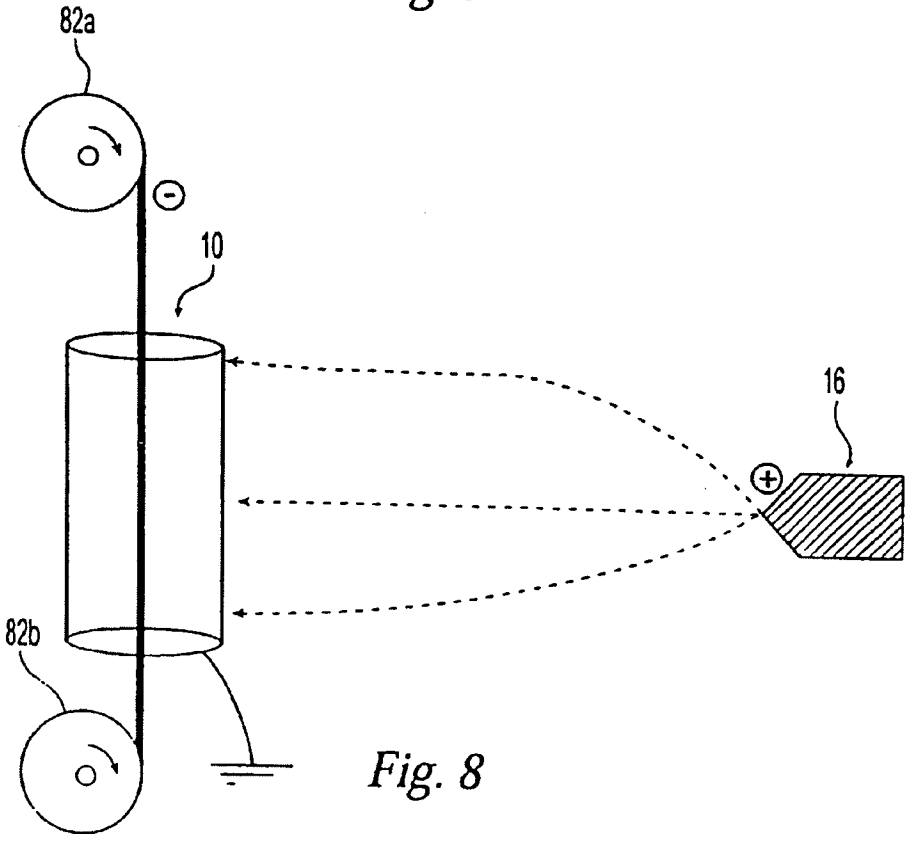


Fig. 8

METHOD FOR SPRAY-COATING A MEDICAL DEVICE HAVING TUBULAR WALL SUCH AS A STENT

This application is a continuation application of U.S. patent application Ser. No. 10/809,765, filed Mar. 24, 2004, now U.S. Pat. No. 6,861,088, which is a continuation application of U.S. patent application Ser. No. 10/109,073, filed Mar. 28, 2002, now U.S. Pat. No. 6,743,463, issued Jun. 1, 2004, all of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

The invention relates generally to a method for coating a stent or a medical device having a tubular wall. More particularly, the invention is directed to a method for electrostatic spray-coating a stent or a medical device having a tubular wall.

BACKGROUND OF THE INVENTION

Medical devices, such as implantable stents, have been coated with a coating comprising a biocompatible polymer to reduce adverse physiological reactions, such as restenosis, caused by uncoated surfaces of medical devices inserted or implanted in patient's body. Also, the coating can incorporate a biologically active material. For example, implanted stents have been used to carry medicinal agents, such as thrombolytic agents. See, U.S. Pat. No. 6,099,562 to Ding et al. U.S. Pat. No. 5,879,697 to Ding et al., Pinchuk to U.S. Pat. No. 5,092,877, U.S. Pat. No. 5,304,121 to Sahatjian.

Such coatings have been applied to the surface of a medical device by various methods, e.g., spray coating and dip coating. When a tubular wall, such as a stent, having openings therein is coated by conventional methods, it has been extremely difficult to coat only the inner surface of a tubular wall without coating the outer surface and vice versa. Also, the ratio of coating thickness placed on the inner surface of the tubular wall and placed on the outer surface of the tubular wall created by a conventional method is fixed and cannot be varied. For example, when a spray coating method is employed to coat such a tubular wall, the ratio of coating thickness depends on the configuration of the tubular wall, specifically, the size and shape of the openings therein. Accordingly, this ratio cannot be controlled. When a dip coating method is employed, the thickness of the coating on the inner surface and the outer surface is the same and cannot be varied. Also, conventional coating methods lack the ability to coat a tubular wall so that the coating thickness along the longitudinal axis of the tubular wall is varied.

Furthermore, in some medical devices having a tubular wall, all of the surfaces of the medical device or portions thereof may not need to be coated, or may not need to be coated with a coating comprising a biologically active material. For instance, the inner surface of a stent does not have to be coated with a coating containing a biologically active material when the biologically active material is intended to be delivered to a body lumen wall, which only directly contacts the outer surface of the stent. The inner surface of the stent does not come in direct contact with the body lumen wall and does not apply the biologically active material to the body lumen wall. On the other hand, if the biologically active material is intended to be delivered to a body fluid rather than a body lumen wall, then the coating containing the biologically active material should be placed on the inner surface of the stent wall but is not needed on the outer surface.

Also, in some instances, a release profile of a biologically active material can be optimized by varying coating thickness along longitudinal axis of the tubular wall. Specifically, in some stents, the amount of a coating containing a biologically active material may be preferably increased at the end sections of the tubular wall or stents as compared to the middle portion to reduce a risk of restenosis caused at the end sections.

In addition, coatings on different portions of the tubular wall may require different physical properties. For example, an expandable stent must be put in its unexpanded state or "crimped" before it is delivered to a body lumen. Thus, the coating on portions of the stent which contact each other in the stent's crimping state must not stick to each other and cause damage. In the case of a balloon expandable stent, the inner surface of the stent that contacts the balloon must not stick to the balloon during expansion. On the other hand, it is desirable to provide a relatively soft or "sticky" coating on the outer surface because it comes in direct contact with a body lumen wall.

Accordingly, there is a need for a method of coating a medical device comprising a tubular wall, such as a stent, that can control the thickness of coating on inner surface and outer surface. Furthermore, there is also a need for a method of coating a tubular wall, such as a stent, that can vary the thickness of coating along the longitudinal axis of the structure.

SUMMARY OF THE INVENTION

This and other objectives are accomplished by the present invention. To achieve these objectives, we have developed a method which is efficient to realize a controlled thickness of a coating on at least a portion of a medical device comprising a tubular wall, such as a stent, having an inner surface, an outer surface and openings therein. Specifically, in the method of the present invention, the tubular wall is grounded or electrically charged, and a conductive core wire is located axially through the tubular wall. A potential is applied to the conductive core wire to impart an electrical charge to the conductive core wire. The tubular wall is exposed to an electrically charged coating formulation, and the charged coating formulation is deposited onto a portion of the tubular wall to form a coating on the tubular wall. In one embodiment, the tubular wall is grounded, and the conductive core wire and the coating formulation has the same electrical charge. In another embodiment, the tubular wall is grounded, and the conductive core wire and the coating formulation has opposite electrical charges. In yet another embodiment, the tubular wall and the coating formulation has the same electrical charge, and the conductive core wire has an electrical charge opposite that of the tubular wall and the coating formulation. Alternatively, the potential applied to the conductive core wire may be pulsated to cyclically impart a positive electrical charge to the conductive core wire followed by a negative electrical charge.

In an embodiment, a core wire comprising a resistor material is located axially through the tubular wall instead of the conductive core wire, and a current is directed in the core wire. Two resistor wires may be located axially through the tubular wall.

Furthermore, in the method of the present invention, the core wire can be kept free of the coating formulation by, for example, using two bobbins, wherein one is feeding the core wire through the tubular wall and the other is winding the core wire. Also, in the method of the present invention, a pair of deflector plates can be used to direct the charged coating formulation.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** depicts a perspective view of a spraying nozzle, particles or droplets of charged coating formulation, a stent and a core wire used in the method of the present invention.

FIGS. **2-4** are illustrative cross-sectional views of a stent and a core wire along with a spray nozzle and representative routes of charged coating formulation in embodiments of the method of the present invention.

FIG. **5** is a graph showing a cyclic change of the electrical potential applied to the core wire in an embodiment of the method of the present invention.

FIGS. **6**A and **6**B are illustrative cross-sectional views of a stent and a core wire along with a spray nozzle and representative routes of the charged coatings formulation for two different states in the embodiment of the method of the present invention shown in FIG. **5**.

FIG. **7** is an illustrative view of a spraying nozzle, a stent, a core wire, a pair of deflector plates, and representative routes of sprayed charged coating formulation, that are arranged for another embodiment of the method of the present invention.

FIG. **8** is an illustrative view of a spraying nozzle, a stent, a core wire, a pair of bobbins, and representative routes of sprayed charged coating formulation in yet another embodiment of the method of the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the method of the present invention, the amount of a coating formulation that is applied to a surface of a stent or tubular wall of a medical device is adjusted by employing the principles of electro-assisted spraying and a core wire located through the stent or tubular wall. The term "tubular wall" refers to a wall having a certain thickness to configured in a shape of a tube or tubular structure. Such tubular structure may have a cross-section other than circle, such as an oval or square. In conventional electro-assisted spraying techniques, an electrically charged coating formulation is sprayed or applied to the surface of the device to be coated. The device is usually grounded or negatively charged. Since the coating formulation is a poor conductor, part of the electrical charge of the coating formulation is unable to escape. Therefore, those portions of the device surface that are coated with the coating formulation will have a higher potential than uncoated regions, and new particles or droplets of charged coating formulation applied to the device will be deflected to those uncoated regions of the device surface. In such method, the amount of coating formulation applied to the surface of the device tends to be uniformly spread over the entire surface. In contrast as explained further below, by locating an electrically charged core wire through the stent or tubular wall of the device, the amount of coating formulation applied on different surfaces or parts of a surface of the device can be varied.

In one embodiment of the present invention, the coating formulation is in a form of droplets. In other embodiments of the present invention, the coating formulation is in a form of dry or wet powder-particles.

Referring to FIG. **1**, which depicts a perspective view of an arrangement for the method of the present invention wherein a conductive core wire **12** is located axially through a stent **10**. Preferably, the core wire is located through the geometric center of the stent. A spray nozzle **16** is placed in proximity of the stent **10** and an electrically charged coating formulation **14** is sprayed to the stent **10**.

In an embodiment shown in FIG. **2**, a stent **10** comprises a stent wall **21** having an inner surface **22**, an outer surface **24** and openings therein **23**. The stent wall **21** is grounded by a ground line so that it becomes electrically neutral. A potential is applied to a conductive core wire **26** located axially through the geometric center of the stent **10** to impart a positive electrical charge to the conductive core wire **26**. The coating formulation is positively charged and sprayed from the nozzle **16** toward the stent **10**. Because of its positive electrical charge, the sprayed coating formulation is attracted to the grounded stent **10** and is deposited on the outer surface **24** and side portions of the openings **23** of the stent wall **21**. Representative routes of the sprayed charged coating formulation are shown as the arrows **28**. The positively charged coating formulation does not enter the openings **23** due to the electrical repulsion of the positively charged core wire. Therefore, the electrically charged coating formulation is deposited only on the outer surface **24** and the side portions of the openings **23** of the stent wall **21**, and the inner surface **22** of the stent wall **21** is maintained substantially free of coating.

In an embodiment shows in FIG. **3**, a stent **10** comprises a stent wall **21** having an inner surface **22**, an outer surface **24** and openings therein **23**. The stent wall **21** is grounded by a ground line so that it becomes electrically neutral. A conductive core wire **26** located axially through the geometric center of the stent **10** is negatively charged. The coating formulation is positively charged and sprayed from the nozzle **16** toward the stent **10**. Because of its positive electrical charge, the sprayed coating formulation is attracted to the grounded stent wall **21**. Some of the coating formulation is deposited on the outer surface **24** of the stent wall **21**, and some of the coating formulation passes through the openings **23**. Representative routes of the coating formulation are shown as the arrows **38**. When the electrically charged coating formulation enters the openings **23**, it is accelerated by virtue of the electrical forces of attraction and are attracted toward the conductive core wire **26**. Therefore, the coating formulation is deposited only on the outer surface **24** of the stent wall **21**, and the side portion of the openings **23** and the inner surface **22** of the stent are maintained substantially free of coating.

The embodiment shown in FIG. **4** is ilustrative of how the method of the invention can be used to control how much coating is applied to the surface of a stent or a tubular wall. In this embodiment, a stent **10** comprises a stent wall **21** having an inner surface **22**, an outer surface **24** and openings therein **23**. The stent wall **21** is positively charged although its electrical potential is not high. A conductive core wire **26** located axially through the geometric center of the stent **10** is negatively charged. The coating formulation is positively charged and sprayed from the nozzle **16** toward the stunt **10**. Because of its positive electrical charge, although the coating formulation is sprayed toward the stent **10**, it is repelled by the positively charged stent **10**. Representative routes of the coating formulation are shown as the arrows **48**. When the coating formulation enters the openings **23**, the coating formulation is attracted to the negatively charged conductive core wire **16** as shown by arrows **47**. Therefore, the coating formulation is not deposited either on the inner surface **22** or on the outer surface **24** of the stent wall **21**, and the stent is maintained substantially free of coating. This embodiment may be used to stop further coating, formulation from being deposited, for example, when a certain amount of coating has been reached. Also, this embodiment may be used to temporally stop coating the device for a period without stopping a continuous stable output from the nozzle.

In an embodiment shown in FIGS. **6**A and **6**B, a stent **10** comprises a stent wall **21** having an inner surface **22**, an outer

surface **24** and openings therein **23**. The stent wall **21** is positively charged although its electrical potential is not high. A conductive core wire **26** is located axially through the geometric center of the stent **10**. The coating formulation is positively charged and sprayed from the nozzle **16** toward the stent **10**. The electrical potential applied to the conductive core wire **26** is repeatedly alternatived between positive and negative as shown in the graph of FIG. **5**. In FIG. **5**, at first, the electrical potential of the conductive core wire is negative (State A) for a certain period, and changes to positive (State B), and again changes to negative (State A). States A and B are repeated in turn. FIG. **6**A shows State A, wherein the stent wall **21** is positively charged (the electrical potential is not high), and the conductive core wire **26** is negatively charged. The coating formulation is positively charged and sprayed from the nozzle **16** toward the stent **10**. Because of its positive electrical charge, although the coating formulation is sprayed toward the stent **10**, majority of particles or droplets are repelled by the positively charged stent **10** as shown arrows **68**. When particles or droplets of the coating formulation enter in the openings **23**, the particles or droplets are attracted to the negatively charged conductive core wire **16** as shown by arrows **67**. Therefore, the coating formulation are not deposited either on the inner surface **22** or on the outer surface **24** of the stent wall **21**, and the stent is maintained substantially free of coating.

FIG. **6**B shows State B, wherein the stent wall **21** is still positively charged as in State A, but the conductive core wire **26** is also positively charged. The electrical potential of the conductive core wire **26** is higher than that of the stent wall **21**. The coating formulation is positively charged and sprayed from the nozzle **16** toward the stent **10**. Because of its positive electrical charge, although the coating formulation is sprayed toward the stent **10**, it is repelled by the positively charged stent **10** as shown by arrows **65**. However, there is the coating formulation inside the stent **10** which was being attracted to but had not yet reached the then-negatively charged conductive core wire **26** in State A. The coating formulation inside the stent **10** is repelled by the core wire **26**, which is now positively charged, and the coating formulation is deposited on the inner surface **22** of the stent wall **21** in State B. Therefore, in this embodiment, the coating formulation is deposited on the inner surface **22**, and the outer surface **24** of the stent wall **21** is maintained substantially free of coating. Skilled artisans can optimize the electrical potentials (voltage) of the conductive core wire **26**, the stent **10** and the coating formulation and the cycle (frequency) of the potential change to adjust the amount of coating applied to the inner surface **22** of the stent wall **21**. Generally, the time period of State A is longer than that of State B. The period of State A is preferably long enough for sufficient amount of coating formulation to enter in the stent wall **21** through the openings **23** but shorter than necessary for the coating formulation to reach the conductive core wire **26**. The period of State B is preferably not more than enough for substantially all coating formulation inside the stent wall **21** to be deposited on the inner surface **22** of the stent wall **21**.

Each embodiment of the method of the present invention explained above can be conducted alone. The embodiment shown in FIG. **2** can be used to coat the outer surface and the side portions of the openings of a stent wall. The embodiment shown in FIG. **3** can be used to coat the outer surface of a stent wall. The embodiment shown in FIGS. **6**A and **6**B can be used to coat the inner surface of a stent wall.

Also, however, those embodiments may be combined, if desired. Particularly, the electrical potential applied to the stent wall may be repeatedly alternated between neutral and positive, and so may the electrical potential applied to the conductive core wire. By adjusting the frequency of the alternation and each electrical potential (voltage), it is possible to obtain any ratio of coating thickness on the inner surface, the outer surface and the side portions of the openings of the stent wall by using a continuous flow of sprayed coating formulation. For example, the following states may be employed to coat the device. Each state is part of a cycle, which can be repeated. During each of the states, the coating formulation remains positively charged:

- State A: The stent wall has a positive electrical charge, but the potential applied to it is lower than that of the coating formulation. The conductive core wire has a negative electrical charge. (See FIG. **6**A)
- State B: The stent wall has a positive electrical charge, and the conductive core wire has a positive electrical charge. The potential of the stent wall is lower than that of the coating formulation and the conductive core wire. (See FIG. **6**B)
- State C: The stent wall is grounded, and the conductive core wire has a positive electrical charge. (See FIG. **2**)
- State D: The stent wall is grounded, and the conductive core wire has a negative electrical charge. (See FIG. **3**)
- State E: The stent wall has a positive electrical charge, but the potential applied to it is lower than that of the coating formulation. The conductive core wire has a negative electrical charge. (See FIG. **4**)

For example, arrangement of each electrical potential can be periodically switched starting from State A and changed to B, C, D, E and returning to A. During the period of States A-B, the coating formulation is deposited to the inner surface of the stent wall. During the period of State C, the coating formulation is deposited to the outer surface and side of the openings of the stent wall. Then, during the period of State D, the coating formulation is deposited to the outer surface of the stent wall, and during the period of State E, the coating formulation is not deposited to the stent wall. To increase the amount of coating placed on the inner surface, the length of time in States A+B should be increased. Likewise, to increase the amount of coating placed on the outer surface, the period of time in States C+D should be increased.

Moreover, the coating formulation may be negatively charged instead of being positively charged. If the coating formulation is negatively charged, then the stent is grounded or negatively charged, and the electrical potentials of the conductive core wire explained in the above embodiments are reversed.

Further, by adjusting time necessary for the coating formulation to reach to the surface to be coated in the above embodiments, it is possible to control the wetness of the coating formulation that arrive at a surface. The time can be adjusted by increasing or decreasing the field strength, specifically the electrical potentials of the coating formulation, the stent and the conductive core wire. If it takes longer for the coating formulation to get from the nozzle to the surface, then the coating formulation is dryer when it reaches the surface. If it takes less time for the coating formulation to get from nozzle to the surface, then the coating formulation is wetter when it reaches the surface. An appropriate wetness of the coating formulation must be chosen to obtain a coating layer which has desired physical properties and desired release profile of the biologically active material. For example, by choosing an appropriate wetness of the coating formulation in liquid form, it is possible to control the coating porosity. Such ability to control porosity is useful for preparing a coating for release a biologically active material.

In embodiments of the method of the present invention, a stent can be coated with a multiple coating layers of the same coating formulation. Such coating layers may be made by using the above mentioned method repeatedly. The thickness of each coating layer can be controlled as explained above. Also, the coating comprises various coating layers of different coating formulations. Such different coating layers can be efficiently made by using the present invention. For example, a first nozzle containing a first coating formulation may be first used to coat the outer surface of a stent by the above-mentioned embodiment of the method of the present invention, and then a second nozzle containing a second coating formulation may be used to coat the outer surface which is already coated with the first coating formulation. If desired, it is possible to coat a surface with the first coating formulation and coat the other surface with the second coating formulation which is different from the first coating formulation.

In addition to controlling the ratio of coating thickness on the inner surface, the outer surface and the side portions of the openings of the stent wall, the coating thickness along the longitudinal axis of a stent or a tubular wall can be controlled by an embodiment of the method of the present invention. Referring to FIG. **7**, a pair of deflector plates **72***a* and **72***b* are added to an embodiment of the present invention shown in FIG. **3**. The pair of deflector plates are a first deflector plate **72***a* having a negative electrical charge and a second deflector plate **72***b* having a positive electrical charge, which are parallel to each other. The pair of deflector plates **72***a*, **72***b* are placed parallel to the direction in which the coating formulation is sprayed from the nozzle **16** toward the stent **10**. The positively charged coating formulation is attracted to the negatively charged deflector plate **72***a* and the course of the charged coating formulation is deflected toward the deflector plate **72***a* as shown by arrow **77**. However, the electrical potential between the deflector plates **72***a* and **72***b* is so small that a majority of particles or droplets of the coating formulation do not contact the negatively charged deflector plate **72***a*. The distribution of the coating formulation on the stent wall **21** in its longitudinal direction can be controlled by using the deflector plates. For example, a stent having a coating which covers only one edge or end section of the stent can be obtained. If the potential is reversed, then the other edge or end section will also be covered by the coating, and a stent having a thicker coating at both end sections and thinner coating in the middle section can be obtained. The term "end section" of the outer surface refers to that part of the surface which extends from an end section or edge of a stent or a tubular wall up to about 25%, preferably from about 3% to about 20% of the entire length of the outer surface. The term "middle section" refers to the remainder of the outer surface that is surrounded by the end sections as defined above.

When the potential is reversed, the coating formulation may be switched from the first coating formulation to the second coating formulation may be switched from the first coating formulation to the second coating formulation so that a tubular wall can have a different type of coating on its end sections. By using different electrical potentials and varying the time such potentials are applied, sophisticated control of the coating can be achieved. For example, coating only a horizontal belt-like portion of the tubular wall or horizontal stripes of the tubular wall, is possible by adjusting the potential between the pair of deflector plates and adjusting the position of the deflector plates relative to the tubular wall.

When the electrical charge of the conductive core wire is opposite to that of the sprayed coating formulation, the coating formulation can be deposited on the conductive core wire in the method of the present invention. Since the coating formulation has poor conductivity, the electrical potential of the wire becomes weaker as more coating formulation accumulates on the wire. To prevent such weakening potential of the conductive core wire, the wire is preferably kept substantially free from the coating formulation. For example, a pair of bobbins can be used to feed new % conductive core wire through a stent as shown in FIG. **8**. A first bobbin **82***a* on which a substantial length of conductive core wire is wound is one side of the stent **10** and the conductive core wire **26** is passed axially through the stent **10** and the other end section of the conductive core wire **26** is connected to a second bobbin **82***b*. As a portion of the conductive core wire is constantly unwound from the first bobbin **82***a* and fed through the stent **10**, the conductive core wire covered with the coating formulation is removed and connected to the second bobbin **82***b*.

In one embodiment of the method of the present invention, a core wire made of a resistor material is used instead of a conductive core wire, and a current is directed through the wire. Since the potential of the core wire comprised of a resistor material is a function of the longitudinal position along the core wire, more electrically charged coating formulation is deposited on the portion of the surface of the tubular wall that is closer to the part of the core wire having higher opposite potential to the charged coating formulation. If two parallel core wires of resistor material are provided in a stent wherein opposing currents are directed, a stent having thicker coating at both end sections and thinner coating in the middle section can be obtained. A pair of bobbins or a pair of deflector plates explained above can also be used for core wires made of a resistor material.

Although the above embodiments of the method of the present invention are explained using a stent as an example of a medical device having a tubular wall, the method of the present invention can be used generally for coating at least a portion of a surface of a medical device comprising a tubular wall having an inner surface and an outer surface and openings therein. A preferable medical device is designed to be inserted or implanted into the body of a patient. Such medical devices suitable for the present invention include, but are not limited to, stents, vascular or other grafts, and filters, such as blood filters.

Medical devices which are particularly suitable for the present invention include stents, for example, vascular stents such as self-expanding stents and balloon expandable stents. Stents suitable for the present invention include any stent for medical purposes, which are known to the skilled artisans. Particularly the method of the present invention is useful for coating stents having intricate surfaces. Examples of self-expanding stents useful in the present invention are illustrated in U.S. Pat. Nos. 4,655,771 and 4,954,126 issued to Wallsten and U.S. Pat. No. 5,061,275 issued to Wallsten et al. Examples of appropriate balloon-expandable stents are shown in U.S. Pat. No. 5,449,373 issued to Pinchasik et al.

The medical devices suitable for the present invention may be fabricated from conductive materials, such as conductive ceramic, polymeric and metallic materials. The surface(s) of the medical devices to be coated using the process of the present invention should be fabricated from conductive materials. Suitable metallic materials include metals and alloys based on titanium (such as nitinol, nickel titanium alloys, thermo-memory alloy materials), stainless steel, tantalum, nickel-chrome, or certain cobalt alloys including cobalt-chromium-nickel alloys such as Elgiloy® and Phynox®. Metallic materials also include clad composite filaments, such as those disclosed in WO 94/16646. An example of a suitable ceramic is carbide. Polymers can be used to fabricate the medical

device when they are conductive. These include polymers filled with carbon-nanotubes. Carbon-nanotubes are commercially available, e.g., from CARBOLEX. Only the surface to be coated rather than entire medical device may be fabricated from a conductive material.

The core wire can be made of a conductive material. The surface of core wire should be conductive. Suitable conductive materials include those described materials for the medical device. In an embodiment of the method of the present invention, the core wire is made of a resistor material, such as carbon, a polymer filled with carbon nanotubes.

Any spraying nozzle or spraying device that can spray coating formulation and create particles or droplets of an appropriate size and of appropriate electrical charge is useful for the method of the present invention. Examples of such spraying nozzle are disclosed in U.S. Pat. No. 4,341,347 to DeVittorio, U.S. Pat. No. 4,004,733 to Law, U.S. Pat. No. 4,215,818 to Hopkinson, and U.S. Pat. No. 4,002,777 to Juvinall et al. One preferable example of a spraying nozzle that can be used in the method of the invention is an apparatus for electrohydrodynamic spray-coating that is disclosed in U.S. Pat. No. 4,749,125, to Escallon et al.

Coating formulations that are useful for the method of the present invention may be a solution or a suspension comprises a polymeric material and solvent or may be powder comprising a polymeric material. The polymeric material useful for forming the coating formulation should be ones that are biocompatible and avoids irritation to body tissue. Preferably the polymeric materials are biostable ones, such as polyurethanes, silicones (e.g., polysiloxanes and substituted polysiloxanes), and polyesters. Also preferable as a polymeric material is styrene-isobutylene copolymers. Other polymers which can be used include ones that can be dissolved and cured or polymerized on the medical device or polymers having relatively low melting points that can be blended with biologically active materials. Additional suitable polymers include, thermoplastic elastomers in general, polyolefins, polyisobutylene, ethylene-alphaolefin copolymers, acrylic polymers and copolymers, vinyl halide polymers and copolymers such as polyvinyl chloride, polyvinyl ethers such as polyvinyl methyl ether, polyvinylidene halides such as polyvinylidene fluoride and polyvinylidene chloride, polyacrylonitrile, polyvinyl ketones, polyvinyl aromatics such as polystyrene, polyvinyl esters such as polyvinyl acetate, copolymers of vinyl monomers, copolymers of vinyl monomers and olefins such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS (acrylonitrile-butadiene-styrene) resins, ethylene-vinyl acetate copolymers, polyamides such as Nylon 66, Nylon 12 and polycaprolactone, alkyd resins, polycarbonates, polyoxymethylenes, polyimides, polyethers, epoxy resins, rayon-triacetate, cellulose, cellulose acetate, cellulose butyrate, cellulose acetate butyrate, cellophane, cellulose nitrate, cellulose propionate, cellulose ethers, carboxymethyl cellulose, collagens, chitins, polylactic acid, polyglycolic acid, polylactic acid-polyethylene oxide copolymers, EPDM (etylene-propylene-diene) rubbers, fluorosilicones, polyethylene glycol, polysaccharides, phospholipids, combinations of the foregoing.

More preferably for medical devices which undergo mechanical challenges, e.g. expansion and contraction, the polymeric materials should be selected from elastomeric polymers such as silicones (e.g. polysiloxanes and substituted polysiloxanes), polyurethanes, thermoplastic elastomers, ethylene vinyl acetate copolymers, polyolefin elastomers, and EPDM rubbers. Because of the elastic nature of these polymers, the coating adheres better to the surface of the medical device when the device is subjected to forces, stress or mechanical challenge.

Furthermore, although the invention can be practiced by using a single type of polymer to form the coating layer(s), various combinations of polymers can be employed. The appropriate mixture of polymers can be coordinated with biologically active materials of interest to produce desired effects when coated on a medical device in accordance with the invention.

Coating formulations useful for the present invention may contain a nanocomposite instead of or in addition to a polymeric material explained above. "Nanocomposite" is a term of art that refers to a composition comprising a polymeric material and relatively small amounts (generally less than about 10% by weight) of nanometer-sized (average size smaller than 1 micrometer) mineral clay or nanosized ceramic particles dispersed therein. Sometimes nanocomposites are refered to as "nanoclay" or "nanoceramic". For example, nanocomposites are disclosed in WO 931014118, U.S. Pat. Nos. 5,385,776, and 6,251,980.

Solvents suitable for forming the coating formulation are ones which can dissolve the polymeric material into solution or form dispersions of the polymeric material in the solvent. Any solvent which does not alter or adversely impact the therapeutic properties of the biologically active material can be employed in the method of the present invention. Examples of useful solvents include tetrahydrofuran, chloroform, toluene, acetone, isooctane, 1,1,1,-trichloroethane, and mixture thereof. Preferably, chloroform or tetrahydrofuran is used as the solvent in the method of the present invention.

Coating formulations useful for the present invention that are in powder form can comprise a polymeric material as explained above. The powder is preferably comprised of particles having an average diameter from about 0.5 μm to about 250 μm. Generally, the resulting surface of the coating is smoother when the powder of the coating formulation used for the coating has a smaller average particle size. After the spray-coating step using the powder coating formulation, the tubular wall coated with the powder coating formulation is heat-treated, for example using IR heating.

Even when the coating formulation used for the present invention contains a solvent, it is possible to control the process to dry the sprayed coating formulation before they reach the tubular wall of the medical device by controlling the method as explained earlier. In this manner, results similar to those of the process using dry-powder coating formulation can be obtained by using the coating formulation containing a solvent.

Coating formulations useful for the method of the present invention may also comprise a biologically active material. The term "biologically active material" encompasses therapeutic agents, such as drugs, and also genetic materials and biological materials, the genetic materials mean DNA or RNA., including, without limitation, of DNA/RNA encoding a useful protein stated below, anti-sense DNA/RNA, intended to be inserted into a human body including viral vectors and non-viral vectors. Examples of DNA suitable for the present invention include DNA encoding

anti-sense RNA

tRNA or rRNA to replace defective or deficient endogenous molecules

angiogenic factors including growth factors, such as acidic and basic fibroblast growth factors, vascular endothelial growth factor, epidermal growth factor, transforming growth factor α and β, platelet-derived endothelial

growth factor, platelet-derived growth factor, tumor necrosis factor α, hepatocyte growth factor and insulin like growth factor

cell ccle inhibitors including CD inhibitors

thymidine kinase ("TK") and other agents useful for interfering with cell proliferation, and

the family of bone morphogenic proteins ("BMP's") as explained below. Viral vectors include adenoviruses, gutted adenoviruses, adeno-associated virus, retroviruses, alpha virus (Semliki Forest, Sindbis, etc.), lentiviruses, herpes simplex virus, ex vivo modified cells (e.g., stem cells, fibroblasts, myoblasts, satellite cells, pericytes, cardiomyocytes, sketetal myocytes, macrophage), replication competent viruses (e.g., ONYX-015), and hybrid vectors. Non-viral vectors include artificial chromosomes and mini-chromosomes, plasmid DNA vectors (e.g., pCOR), cationic polymers (e.g., polyethyleneimine, polyethyleneimine (PEI)) graft copolymers (e.g., polyether-PEI and polyethylene oxide-PEI), neutral polymers PVP, SP1017 (SUPRATEK), lipids or lipoplexes, nanoparticles and microparticles with and without targeting sequences such as the protein transduction domain (PTD).

The biological materials include cells, yeasts, bacteria, proteins, peptides, cytokines and hormones. Examples for peptides and proteins include growth factors (FGF, FGF-1, FGF-2, VEGF, Endotherial Mitogenic Growth Factors, and epidermal growth factors, transforming growth factor α and β, platelet derived endothelial growth factor, platelet derived growth factor, tumor necrosis factor α, hepatocyte growth factor and insulin like growth factor), transcription factors, proteinkinases, CD inhibitors, thymidine kinase, and bone morphogenic proteins (BMP's), such as BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 (Vgr-1), BMP-7 (OP-1), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-14, BMP-15, and BMP-16. Currently preferred BMP's are BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7. Alternatively or in addition, molecules capable of inducing an upstream or downstream effect of a BMP can be provided. Such molecules include any of the "hedgehog" proteins, or the DNA's encoding them. These dimeric proteins can be provided as homodimers, heterodimers, or combinations thereof, alone or together with other molecules. Cells can be of human origin (autologous or allogeneic) or from an animal source (xenogeneic), genetically engineered, if desired, to deliver proteins of interest at the transplant site. The delivery media can be formulated as needed to maintain cell function and viability. Cells include whole bone marrow, bone marrow derived mono-nuclear cells, progenitor cells (e.g., endothelial progentitor cells) stem cells (e.g., mesenchymal, hematopoietic, neuronal), pluripotent stem cells, fibroblasts, macrophage, and satellite cells.

Biologically active material also includes non-genetic therapeutic agents, such as:

anti-thrombogenic agents such as heparin, heparin derivatives, urokinase, and PPack (dextrophenylalanine proline arginine chloromethylketone);

anti-proliferative agents such as enoxaprin, angiopeptin, or monoclonal antibodies capable of blocking smooth muscle cell proliferation, hirudin, and acetylsalicylic acid, amlodipine and doxazosin;

anti-inflammatory agents such as glucocorticoids, betamethasone, dexamethasone, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, and mesalamine;

immunosuppressants such as sirolimus (RAPAMYCIN), tacrolimus, everolimus and dexamethasone,

antineoplastic/antiproliferative/anti-miotic agents such as paclitaxel, 5-fluorouracil, cisplatin, vinblastine, vincristine, epothilones, methotrexate, azathioprine, halofuginone, adriamycin, actinomycin and mutamycin; endostatin, angiostatin and thymidine kinase inhibitors, and its analogs or derivatives;

anesthetic agents such as lidocaine, bupivacaine, and ropivacaine;

anti-coagulants such as D-Phe-Pro-Arg chloromethyl keton, an RGD peptide-containing compound, heparin, antithrombin compounds, platelet receptor antagonists, anti-thrombin anticodies, anti-platelet receptor antibodies, aspirin (aspirin is also classified as an analgesic, antipyretic and anti-inflammatory drug),dipyridamole, protamine, hirudin, prostaglandin inhibitors, platelet inhibitors and tick antiplatelet peptides;

vascular cell growth promotors such as growth factors. Vascular Endothelial Growth Factors (FEGF, all types including VEGF-2), growth factor receptors, transcriptional activators, and translational promotors;

vascular cell growth inhibitors such as antiproliferative agents, growth factor inhibitors, growth factor receptor antagonists, transcriptional repressors, translational repressors, replication inhibitors, inhibitory antibodies, antibodies directed against growth factors, bifunctional molecules consisting of a growth factor and a cytotoxin, bifunctional molecules consisting of antibody and a cytotoxin;

cholesterol-lowering agents; vasodilating agents; and agents which interfere with endogenous vasoactive mechanisms;

anti-oxidants, such as probucol;

antibiotic agents, such as penicillin, cefoxitin, oxacillin, tobranycin

angiogenic substances, such as acidic and basic fibrobrast growth factors, estrogen including estradiol (E2), estriol (E3) and 17-Beta Estradiol; and

drugs for heart failure, such as digoxin, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors including captopril and enalopril.

Also, the biologically active materials of the present invention include nitric oxide adducts, which prevent and/or treat adverse effects associated with use of a medical device in a patient, such as restenosis and damaged blood vessel surface. Typical nitric oxide adducts include nitroglycerin, sodium nitroprusside, S-nitroso-proteins, S-nitroso-thiols, long carbon-chain lipophilic S-nitrosothiols, S-nitrosodithiols, iron-nitrosyl compounds, thionitrates, thionitrites, sydnonimines, furoxans, organic nitrates, and nitrosated amino acids, preferably mono- or poly-nitrosylated proteins, particularly polynitrosated albumin or polymers or aggregates thereof. The albumin is preferably human or bovine, including humanized bovine serum albumin. Such nitric oxide adducts are disclosed in U.S. Pat. No. 6,087,479 to Stamler et al. which is incorporated herein by reference.

A biologically active material may be encapsulated in micro or nano-capsules by the known methods.

The biologically active material can be used with (a) biologically non-active material(s) including a carrier or an excipient, such as sucrose acetate isobutyrate (SABER™ commercially available from SBS) ethanol, n-methyl pymolidone, dimethyl sulfoxide, benzyl benxoate, benzyl acetate, albumine, carbohydrate, and polysacharide. Also, nanoparticles of the biologically active materials and non-active materials are useful for the coating formulation of the present invention.

The description contained herein is for purposes of illustration and not for purposes of limitation. Changes and modifications may be made to the embodiments of the description and still be within the scope of the invention. Furthermore, obvious changes, modifications or variations will occur to those skilled in the art. Also, all references cited above are incorporated herein, in their entirety, for all purposes related to this disclosure.

We claim:

1. A method for coating a medical device comprising a tubular wall having an inner surface, an outer surface and openings therein, wherein the method comprises:

(a) charging the tubular wall with a positive electrical charge;

(b) providing a conductive core wire located axially through the tubular wall;

(c) applying a potential to the conductive core wire to impart an electrical charge to the conductive core wire;

(d) exposing the tubular wall to an electrically charged coating formulation, wherein the electrical charge of the coating formulation is opposite of the electrical charge of the core wire; and

(e) depositing the coating formulation onto a portion of the tubular wall to form a coating on the tubular wall.

2. The method of claim **1**, wherein the coating formulation comprises a polymeric material and a solvent.

3. The method of claim **2**, wherein the coating formulation further comprises a biologically active material.

4. The method of claim **3**, wherein the biologically active material comprises an immunosuppressant, an antiproliferative agent, or a combination thereof.

5. The method of claim **4**, wherein the immunosuppressant comprises sirolimus, everolimus, tacrolimus, or a combination thereof.

6. The method of claim **4**, wherein the antiproliferative agent comprises paclitaxel, an analog thereof, a derivative thereof, or a combination thereof.

7. The method of claim **1**, wherein the conductive core wire has the opposite electrical charge as the tubular wall.

8. The method of claim **1**, wherein the electrical charge of the conductive core wire is adjusted so that the charged coating formulation is deposited on the inner surface of thetubular wall and the outer surface remains substantially free of the charged coating formulation.

9. The method of claim **1**, wherein the tubular wall comprises a geometric center, and the conductive core wire is located axially through the center of the tubular wall.

10. The method of claim **1**, wherein the potential applied to the conductive core wire is pulsated to cyclically impart a positive electrical charge to the conductive core wire followed by a negative electrical charge.

11. The method of claim **10**, wherein a positive electrical charge imparted to the conductive core wire is for a shorter duration than the negative electrical charge imparted to the conductive core wire.

12. The method of claim **1**, wherein the conductive core wire has two ends and one end of the conductive core wire is connected to a first bobbin and the other end is connected to a second bobbin, wherein the conductive core wire is fed from the first bobbin through the tubular wall, and wherein the conductive core wire covered with the coating formulation is removed from the tubular wall by being connected to the second bobbin.

13. The method of claim **1**, which further comprises directing the charged coating formulation by: (a) providing a first deflector plate having a positive electrical charge and a second deflector plate having a negative electrical charge, wherein the plates are placed parallel to each other; and (b) applying the charged coating formulation between the plates.

14. A method for coating a medical device comprising a tubular wall having an inner surface, an outer surface and openings therein, wherein the method comprises:

(a) charging the tubular wall with a positive electrical charge;

(b) providing a first core wire comprising a resistor material located axially through the tubular wall;

(c) directing a current through the first core wire;

(d) creating an electrically charged coating formulation, wherein the electrical charge is positive; and

(e) depositing the coating formulation onto the tubular wall to form a coating on the tubular wall.

15. The method of claim **14**, wherein the coating formulation further comprises a polymeric material and a solvent.

16. The method of claim **15**, wherein the coating formulation further comprises a biologically active material.

17. The method of claim **16**, wherein the biologically active material comprises an immunosuppressant, an antiproliferative agent, or a combination thereof.

18. The method of claim **17**, wherein the immunosuppressant comprises sirolimus, everolimus, tacrolimus, or a combination thereof.

19. The method of claim **16**, wherein the antiproliferative agent comprises paclitaxel, an analog thereof, a derivative thereof, or a combination thereof.

20. The method of claim **14**, wherein the inner surface of the tubular wall comprises two end sections and wherein a greater amount of coating formulation is applied to one end section than the other.

21. The method of claim **14**, which further comprises providing a second core wire comprising a resistor material through the tubular wall wherein the second core wire is parallel to the first core wire; and directing a second current through the second core wire in a direction opposite the first current.

22. The method of claim **14**, wherein the first core wire comprising two ends and one end of the first core wire is connected to a first bobbin and the other end is connected to a second bobbin, wherein the first core wire is fed from the first bobbin through the tubular wall, and wherein the first core wire covered with the coating formulation is removed from the tubular wall by being connected to the second bobbin.

23. A method for coating at least a portion of a stent, wherein the stent comprises a stent wall having an inner surface, an outer surface and openings therein, wherein the method comprises:

(a) charging the stent wall with a positive electrical charge;

(b) providing a conductive core wire located axially through the stent;

(c) applying a potential to the conductive core wire to impart an electrical charge to the conductive core wire;

(d) exposing the stent to an electrically charged coating formulation, wherein the electrical charge of the coating formulation is opposite of the electrical charge of the core wire; and

(e) depositing the charged coating formulation onto a portion of the stent form a coating thereon.

24. The method of claim **23**, wherein the coating formulation further comprises a polymeric material and a solvent.

25. The method of claim **24**, wherein the coating formulation further comprises a biologically active material.

26. The method of claim **25**, wherein the biologically active material comprises an immunosuppressant, an antiproliferative agent, or a combination thereof.

27. The method of claim **26**, wherein the immunosuppressant comprises sirolimus, everolimus, tacrolimus, or a combination thereof.

28. The method of claim **26**, wherein the antiproliferative agent comprises paclitaxel, an analog thereof, a derivative thereof, or a combination thereof.

* * * * *

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(12) **United States Patent**
Ding et al.

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(45) **Date of Patent: Feb. 17, 2009**

(54) **PURIFIED POLYMERS FOR COATINGS OF IMPLANTABLE MEDICAL DEVICES**

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A61F 2/06 (2006.01)

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(58) **Field of Classification Search** 623/1.14, 623/1.18, 1.21, 1.42, 1.43, 1.46; 427/2.28
See application file for complete search history.

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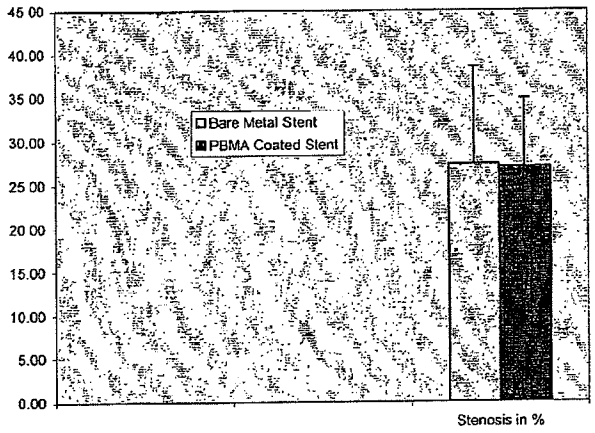
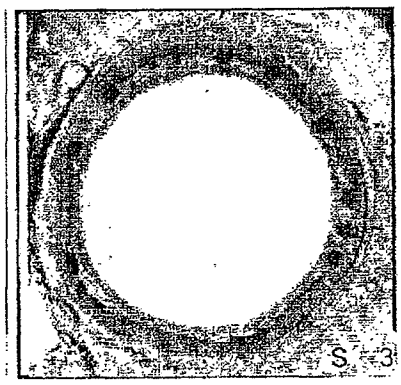
(57) **ABSTRACT**

A coating for a medical device, particularly for a drug eluting stent, is described. The coating includes a purified polymer such as a polyacrylate.

23 Claims, 5 Drawing Sheets





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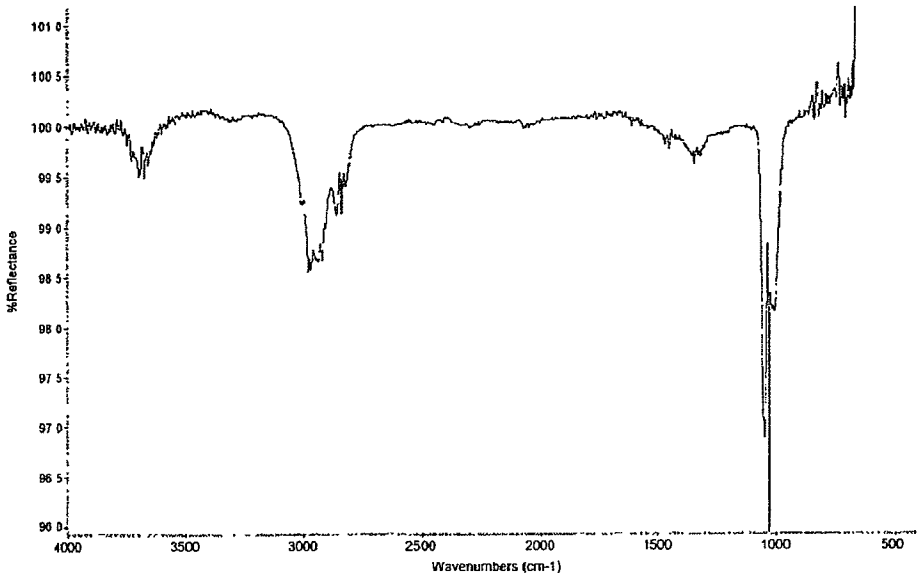
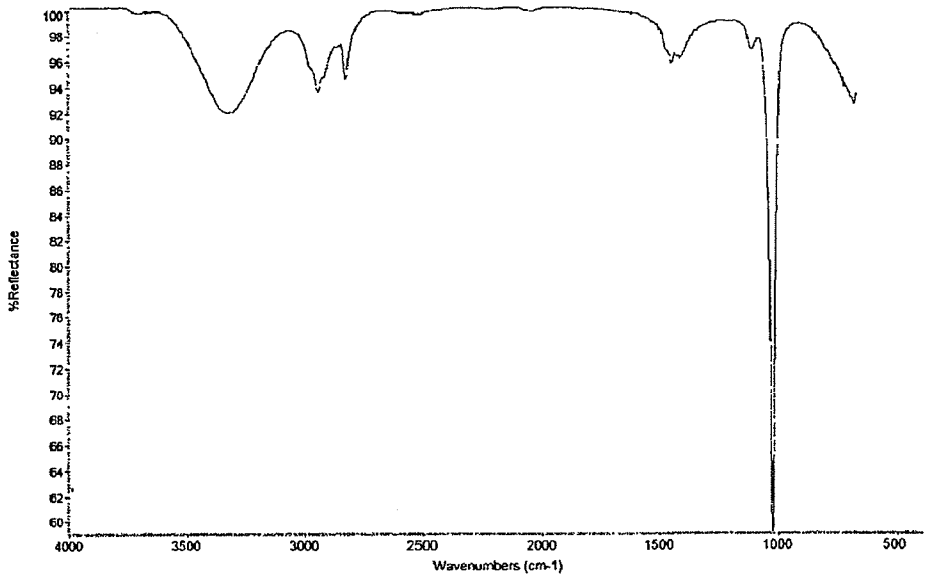


FIGURE 1



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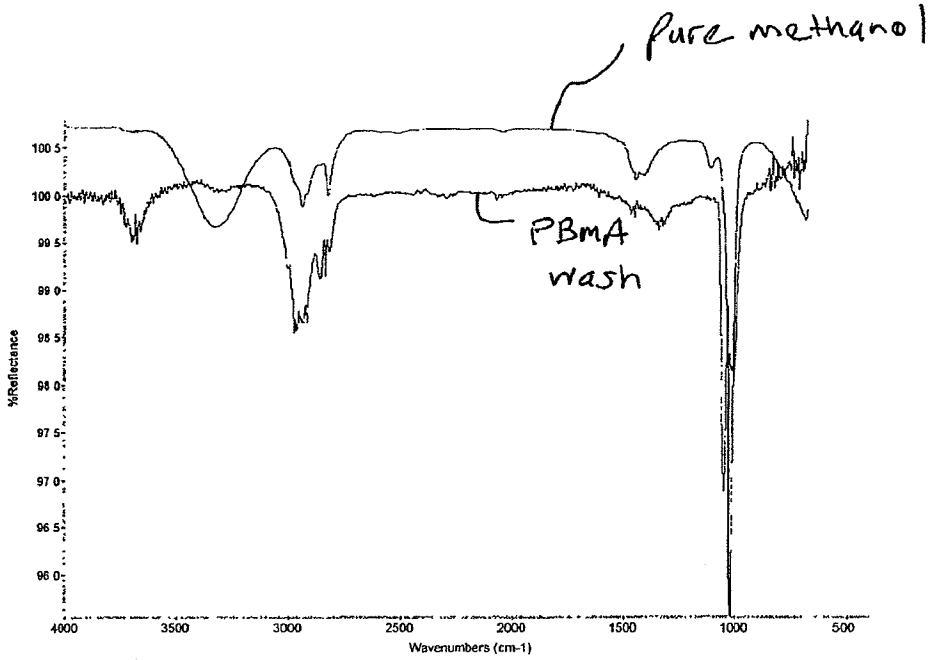

FIGURE 3

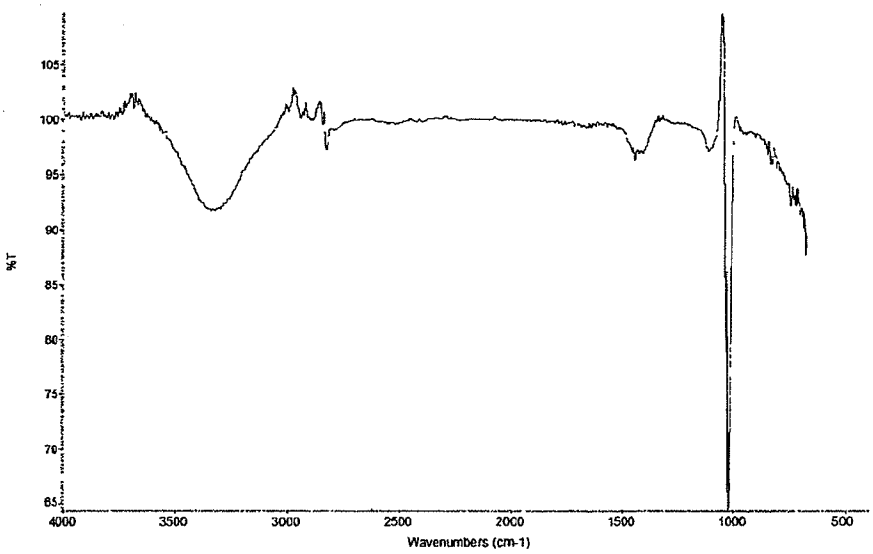

FIGURE 4

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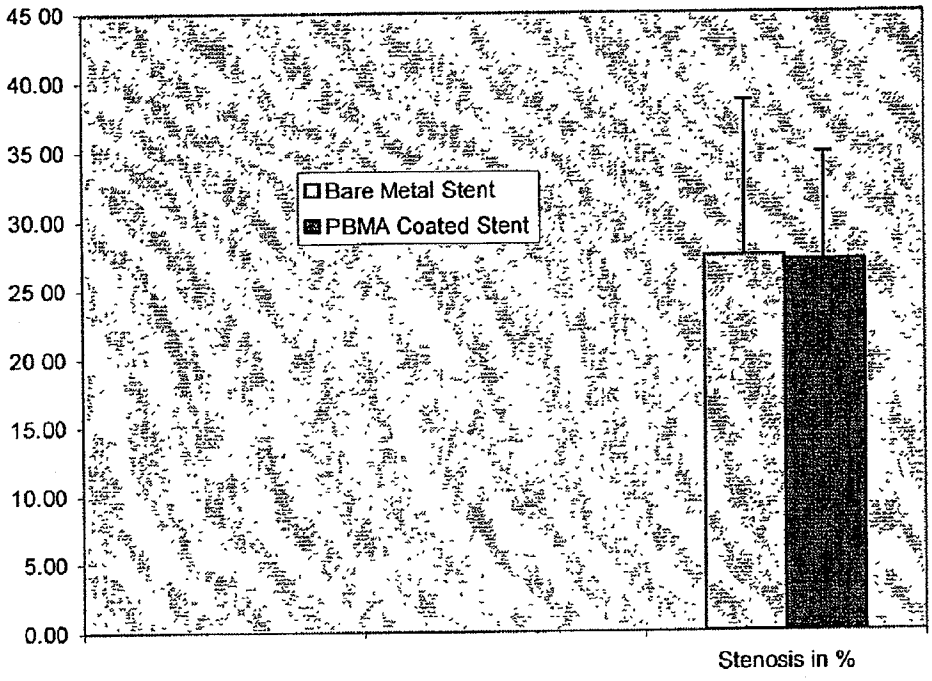
45 00
40.00
35 00
30.00
25 00
20 00
15.00
10.00
5.00
0.00
Bare Metal Stent
PBMA Coated Stent
Stenosis in %

Figure 5

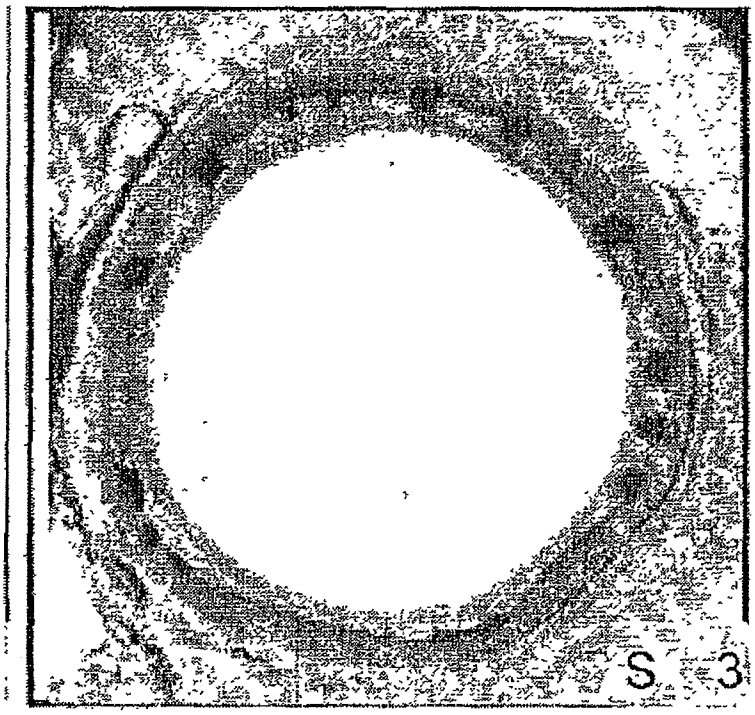

Figure 6

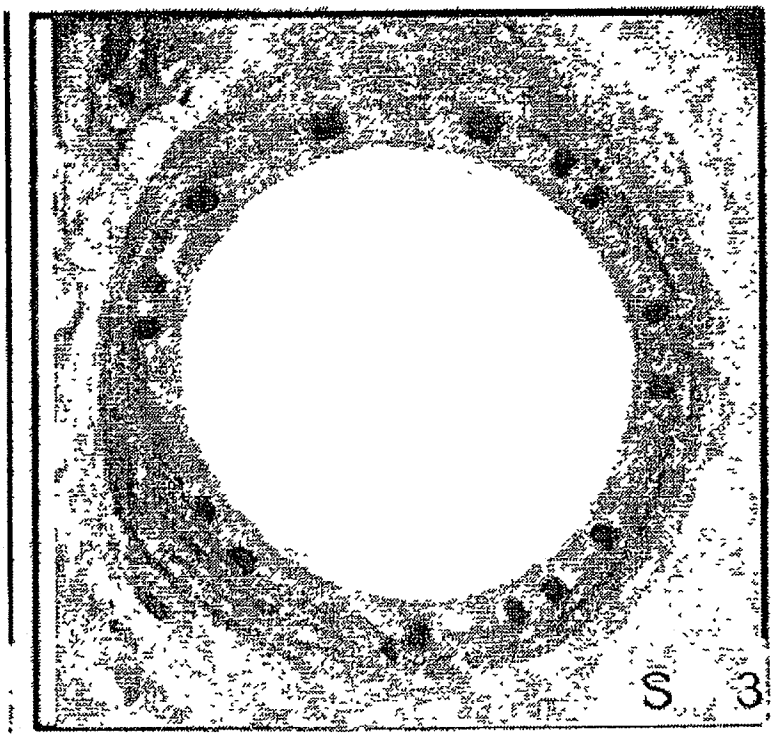

Figure 7

PURIFIED POLYMERS FOR COATINGS OF IMPLANTABLE MEDICAL DEVICES

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention is directed to coatings for implantable medical devices, such as drug eluting vascular stents.

2. Description of the State of the Art

Percutaneous transluminal coronary angioplasty (PTCA) is a procedure for treating heart disease. A catheter assembly having a balloon portion is introduced percutaneously into the cardiovascular system of a patient via the brachial or femoral artery. The catheter assembly is advanced through the coronary vasculature until the balloon portion is positioned across the occlusive lesion. Once in position across the lesion, the balloon is inflated to a predetermined size to radially compress against the atherosclerotic plaque of the lesion to remodel the lumen wall. The balloon is then deflated to a smaller profile to allow the catheter to be withdrawn from the patient's vasculature.

A problem associated with the above procedure includes formation of intimal flaps or torn arterial linings which can collapse and occlude the conduit after the balloon is deflated. Moreover, thrombosis and restenosis of the artery may develop over several months after the procedure, which may require another angioplasty procedure or a surgical by-pass operation. To reduce the partial or total occlusion of the artery by the collapse of arterial lining and to reduce the chance of the development of thrombosis and restenosis, a stent is implanted in the lumen to maintain the vascular patency.

Stents are used not only as a mechanical intervention but also as a vehicle for providing biological therapy. As a mechanical intervention, stents act as scaffoldings, functioning to physically hold open and, if desired, to expand the wall of the passageway. Typically, stents are capable of being compressed, so that they can be inserted through small vessels via catheters, and then expanded to a larger diameter once they are at the desired location.

Biological therapy can be achieved by medicating the stents. Medicated stents provide for the local administration of a therapeutic substance at the diseased site. In order to provide an efficacious concentration to the treated site, systemic administration of such medication often produces adverse or toxic side effects for the patient. Local delivery is a preferred method of treatment in that smaller total levels of medication are administered in comparison to systemic dosages, but are concentrated at a specific site. Local delivery thus produces fewer side effects and achieves more favorable results. One proposed method for medicating stents involves the use of a polymeric carrier coated onto the surface of a stent. A solution which includes a solvent, a polymer dissolved in the solvent, and a therapeutic substance dispersed in the blend is applied to the stent. The solvent is allowed to evaporate, leaving on the stent surface a coating of the polymer and the therapeutic substance impregnated in the polymer.

A potential shortcoming of the foregoing method of medicating stents is that the polymers can contain impurities that trigger adverse biological responses to the stent when implanted into a biological lumen. The polymers can contain impurities such as catalysts, initiators, processing aids, suspension aids, unreacted monomers and oligomers or other low molecular weight species, even though the polymer is sold as a "medical grade" polymer by the manufacturer. Thus, there is a need for a stent coating with purified polymers. The present invention provides a coating to meet this need.

SUMMARY

In accordance with one aspect of the invention, a stent is disclosed that is used for implantation in a vessel of a patient. The stent includes a coating which has a polymeric material which has been purified to be completely or partially free from an impurity or impurities which cause the material to have a greater adverse biological response than the response caused by the material when the impurity or impurities have been removed or reduced from the material. In one embodiment of the invention, the polymeric material is a polyacrylate material. In another embodiment, the polymeric material is a blend of at least two polymers. In a further embodiment, the coating additionally has an active agent.

In accordance with a further aspect of the invention, a method of coating a stent is disclosed, including forming a coating having a polymeric material on the stent, wherein the polymeric material has been purified to remove, or reduce the amount of, an impurity or impurities which cause the material to have a greater adverse biological response than the response caused by the material when the impurity or impurities have been removed or reduced from the material. In one embodiment, the polymeric material is purified by a process including solvent washing, centrifugal cleaning, soxhlet extraction, filtration, step precipitation, centrifugal filtration or a combination thereof.

In a further aspect, a method of coating a stent is disclosed including purifying a polymeric material to partially or completely remove an impurity or impurities which can cause an adverse biological response, adding the purified polymeric material to a solvent to form a composition, applying the composition to the stent, and removing the solvent to form a coating including the purified polymeric material.

In yet another aspect of the present invention, a stent is disclosed with a coating, the coating including a purified polymeric material that has generally the same degree of biological inertness as stainless steel when implanted in a blood vessel of a mammal.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. **1-4** are comparative spectrographs from a Fourier Transform Infrared Spectrophotometer as referred to in Example 2;

FIG. **5** is a graph of percent stenosis from a 28 day animal study as referred to in Example 5; and

FIGS. **6** and **7** are histograms as referred to in Example 5.

DETAILED DESCRIPTION

For ease of discussion, the coatings and methods detailed herein will be described with reference to a coating for a stent. However, the implantable device coated in accordance with embodiments of the present invention may be any suitable medical substrate that can be implanted in a human or veterinary patient. Examples of such implantable devices include self-expandable stents, balloon-expandable stents, stent-grafts, grafts (e.g., aortic grafts), artificial heart valves, cerebrospinal fluid shunts, pacemaker electrodes, and endocardial leads (e.g., FINELINE and ENDOTAK, available from Guidant Corporation). The underlying structure of the device can be of virtually any design. The device can be made of a metallic material or an alloy such as, but not limited to, cobalt chromium alloy (ELGILOY), stainless steel (316L), "MP35N," "MP20N," elastinite (Nitinol), tantalum, nickel-titanium alloy, platinum-iridium alloy, gold, magnesium, or combinations thereof. "MP35N" and "MP20N" are trade

names for alloys of cobalt, nickel, chromium and molybdenum available from standard Press Steel Co., Jenkintown, Pa. "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum. Devices made from bioabsorbable or biostable polymers could also be used with the embodiments of the present invention.

Coating

In an embodiment of the present invention, a stent has a coating that includes a purified polymer. The polymer can be purified by methods detailed herein. The stent can be used for implantation at a selected region of a vessel of a patient for inhibiting restenosis, and can include an active agent. After the polymer has been purified, the polymer is substantially biologically inert. "Purified" refers to a polymer that has had impurities removed or significantly reduced. "Impurities" refer to traces of catalysts, initiators, processing aids, suspension aids, unreacted monomers and oligomers or other low molecular weight species, or any other chemical remaining in the polymer, that can cause or effectuate an adverse biological response greater than which would occur if the impurity is removed or significantly reduced. For example, "medical grade" poly(n-butyl methacrylate) (PBMA) can contain impurities such as suspension aids (e.g., starch) and unreacted monomers. "Biologically inert" refers to a material that does not elicit a significantly greater adverse biological response than a biocompatible material, such as stainless steel, when implanted into a body vessel. Examples of biocompatible materials include metals such as stainless steel, titanium, and Nitinol, and organic materials such as collagen, fibronectin, polyethylene glycol, polysaccharides, TEFLON, silicone and polyurethane. As shown below in Example 5, it has been found that the polymeric coating of the present invention is essentially biologically inert.

The coating for a stent including the purified polymer can have a drug-polymer layer, an optional topcoat layer, and an optional primer layer. The drug-polymer layer can be applied directly onto the stent surface to serve as a reservoir for a therapeutically active agent or drug which is incorporated into the drug-polymer layer. The topcoat layer, which can be essentially free from any therapeutic substances or drugs, serves as a rate limiting-membrane for controlling the rate of release of the drug. The optional primer layer can be applied between the stent and the drug-polymer layer to improve the adhesion of the drug-polymer layer to the stent.

According to one embodiment of the present invention, polymers of esters having the general formula (I):

$$—[CH_2—C(X)(COOR)]_m—[CH_2—C(X')(COOR')]_n —[CH_2—C(X'')(COOR'')]_p—, \quad (I)$$

or blends thereof, can be purified and then used for making the stent coatings.

In formula (I), X, X', and X" are each, independently, a hydrogen atom (acrylates) or an alkyl group, such as a methyl group CH_3 (methacrylates); R, R' and R" are each, independently, a C_1 to C_{12} straight chained or branched aliphatic group, or a hydroxylated aliphatic group; "m" is an integer larger than 1, and "n" and "p" are each 0 or an integer. If both n=0 and p=0, the polymer of formula (I) is a homopolymer (i.e., PBMA). If $n \neq 0$ and p=0, or n=0 and $p \neq 0$, the polymer of formula (I) is a copolymer, and if $n \neq 0$ and $p \neq 0$, the polymer of formula (I) is a terpolymer.

After purification, polymers of formula (I) can be used for making either the drug-polymer layer, the topcoat membrane, the optional primer layer, or any combination thereof. For the purposes of the present invention, such polymers, or blends thereof, are defined as "polyacrylates" or as "polyacrylate materials."

One example of a polyacrylate suitable for fabricating either the drug-polymer layer or the topcoat membrane is PBMA, described by formula (I) where X=CH_3, n=0, p=0, and "R" is a n-butyl radical C_4H_9 (—CH_2—CH_2—CH_2—CH_3). PBMA has good biocompatibility, is soluble in many common solvents, has good mechanical and physical properties, and adheres well to the underlying stent surface or the primer layer. PBMA is available commercially from Aldrich Chemical Co. of Milwaukee, Wis., and from Esschem, Inc. of Lynwood, Pa.

Some examples of polyacrylates that are suitable for purification and fabrication of the coating, e.g., the drug-polymer layer and/or the topcoat membrane, are summarized in Table 1.

TABLE 1

No.	Polyacrylate	Abbreviation	R	X	m	R'	X'	n/m	T_g, ° C.
1	Poly(n-butyl methacrylate)	PBMA	n-C_4H_9	CH_3	>1	N/A	N/A	0	20
2	Poly(iso-butyl methacrylate)	Pi-BMA	i-C_4H_9	CH_3	>1	N/A	N/A	0	66
3	Poly(tert-butyl methacrylate)	Ptert-BMA	tert-C_4H_9	CH_3	>1	N/A	N/A	0	107
4	Poly(methyl methacrylate)	PMMA	CH_3	CH_3	>1	N/A	N/A	0	105
5	Poly(ethyl methacrylate)	PEMA	C_2H_5	CH_3	>1	N/A	N/A	0	63
6	Poly(n-propyl methacrylate)	PPMA	n-C_3H_7	CH_3	>1	N/A	N/A	0	35
7	Poly(methyl acrylate)	PMA	CH_3	H	>1	N/A	N/A	0	9
8	Poly(n-hexyl methacrylate)	PHMA	n-C_6H_{13}	CH_3	>1	N/A	N/A	0	−5
9	Poly(methyl methacrylate-co-n-butyl methacrylate)	P(MMA-BMA)	CH_3	CH_3	>1	n-C_4H_9	CH_3	7/3	46
10	Poly(n-butyl methacrylate-co-iso-butyl methacrylate)	P(BMA-i-BMA)	n-C_4H_9	CH_3	>1	i-C_4H_9	CH_3	1/1	35
11	Poly(n-butyl methacrylate-co-2-hydroxyethyl methacrylate)	P(BMA-HEMA)	n-C_4H_9	CH_3	>1	CH_2CH_2OH	CH_3	7/3	≧25
12	Poly(methyl methacryate-co-2-hydroxyethyl methacrylate)	P(MMA-HEMA)	CH_3	CH_3	>1	CH_2CH_2OH	CH_3	7/3	≧65
13	Poly(ethyl methacrylate-co-2-hydroxyethyl methacylate)	P(EMA-HEMA)	C_2H_5	CH_3	>1	CH_2CH_2OH	CH_3	7/3	>50

Only homo- and copolymers are listed in Table 1 (that is, the polymers of formula (I) where p=0), but it should be understood that terpolymers corresponding to formula (I) (when n≠0 and p≠0) can be used as well. Also, it should be understood that the n/m ratios (from formula (I)) listed in Table 1 are provided by way of example, and other n/m ratios are contemplated to fall within the scope of this invention. For instance, the n/m ratio for P(BMA-HEMA) can also be 95/5.

Methods of Purification

Before the polymer is applied to the stent to form a coating, the polymer should be purified to remove impurities. By using the methods of the present invention, the polymer can be purified to remove a significant amount of residual catalysts, initiators, processing aids, suspension aids, unreacted monomers and oligomers or other low molecular weight species. For example, a polymer mass can be purified by washing the polymer mass with a solvent that dissolves the impurity, but not the polymer. Additionally, the polymer mass can be purified by dissolving the polymer mass in a solvent and subjecting the polymer mass to a centrifuge. According to other embodiments, the polymers can be purified by soxhlet extraction, filtration, step precipitation, and centrifugal filtration.

Solvent Washing

A solvent can be used to wash the impurities from the polymer. The impurities, such as low molecular species including unreacted monomers and oligomers, should be miscible in the solvent, while the polymer should be immiscible in the solvent. Representative examples of polymer-solvent pairs include using methanol for PBMA, ethanol for PMMA, acetonitrile or hexane for PEMA and methanol for P(BMA-HEMA).

The polymer should be mixed with the solvent and stirred. Sonication can also be used to mix the components. The polymer and solvent can be mixed for a few minutes to several hours, for example, from 1 to 16 hours. Usefully, the mixture is agitated for a relatively longer period to remove certain impurities. The mixed solvent can be replaced by fresh solvent so that the polymer can be washed multiple times. After the washing process is complete, the polymer is then dried (e.g., by vacuum drying) to remove the solvent from the polymer.

Centrifugal Cleaning

The polymer can also be purified by using a centrifuge if the impurity has a higher density than the polymer solution. The polymer is first substantially dissolved in a solvent. By way of example, PBMA can be dissolved in acetone. Usefully, for many polymers, the solvent is a low density solvent (e.g., tetrahydrofuran (THF) or ethyl acetate). Many high density solvents such as chloroform, may not be useful for this particular process. Representative examples of polymer-solvent pairs include using ethyl acetate for PEMA, methyl ethyl ketone for PMMA and THF for P(BMA-HEMA).

After the polymer is dissolved in the solvent, the solution is centrifuged for about 10 minutes to 1 hour. The supernatant is carefully collected and the precipitate at the bottom of the centrifuge tubing, which contains impurities, is then removed from the solution. It is preferred that the solvent used for this process is the same solvent used for the stent coating process described in detail below. Also, it is preferred to use this centrifugal cleaning process subsequent to the solvent washing process.

Filtration

Instead of using a centrifuge, impurities can be removed from the polymer by using filtration. The polymer should first be substantially dissolved in a solvent. The solvents useful for the centrifugal cleaning process are also useful for this process. The solution is then run through a filter connected to a vacuum pump to remove the impurities that do not dissolve with the polymer. The filter used should have a pore size large enough to allow the passage of the polymer, but small enough to remove the impurities from the solution. Representative examples of pore sizes for filters include 1-10 μm.

Soxhlet Extraction

A soxhlet extraction can also be used to remove impurities from the polymer, especially if the T_g of the polymer is relatively high (e.g., Pi-BMA, PMMA and PEMA). First, a polymer is placed into a glass extraction tube and the tube is placed inside an extraction apparatus. A solvent is mixed with the polymer. The solvent should be incompatible with the polymer (i.e., does not dissolve the polymer), but should be compatible with one or more impurities. The solvent may cause the polymer to partially swell. Also, typically, the solvent will have a boiling temperature that is below or equal to the T_g of the polymer. In this process, the solvent serves as the extraction medium. Representative examples of polymer-solvent pairs include using methanol for Pi-BMA, ethanol or acetonitrile:methanol (50:50 wt/wt) for PMMA, hexane for PEMA and FLUX REMOVER AMS for P(BMA-HEMA). After the polymer has been put into solution, a heating source is used to warm the solvent to generate vapor. The solvent vapor removes low molecular weight species from the polymer.

It has been found that if the temperature exposed to the extraction apparatus is too close to the T_g of the polymer, the polymer can swell and block the filters used in the extraction apparatus. As a result, it may be useful to cool portions of the extraction apparatus (e.g., extraction tube) during the process to prevent polymer swelling.

Step Precipitation

The polymer can also be purified by using a step precipitation process. A polymer mass should first be substantially dissolved in a compatible solvent. While the solution is stirred, an incompatible solvent is gradually added to the solution so that polymer precipitates. The polymer is then recovered and dried. The impurities that were in the polymer before the process remain in the solution. In an embodiment, step precipitation is used after centrifugal cleaning wherein the polymer remains dissolved in the solvent used for the centrifugal cleaning process before addition of the incompatible solvents. The following are representative examples of polymer-solvent pairings:

TABLE 2

Polymer	Compatible Solvent(s)	Incompatible Solvent(s)
PBMA	Acetone	Water or Heptane
PEMA	THF	Methanol
P(BMA-HEMA)	THF	Water

Centrifugal Filtration

Impurities can also be removed by centrifugal filtration. This method was originally developed for the removal of cells and particulates from nucleic acids, proteins, and enzymes, and has been adapted for the present invention to remove lower molecular weight fractions from a polymer. First, the polymer is dissolved in a solvent. Then the solution is placed in a centrifugal filtration unit (such as Centriplus-100, avail-

able from Millipore, Medford, Mass.) which is run in a centrifuge (e.g., available from Sorvall, Newtown, Conn.). The filtration unit should be compatible with the solvent used to dissolve the polymer. In one embodiment, the polymer is first subjected to the centrifugal cleaning process, and then further purified by being placed in the centrifugal filtration apparatus.

Method of Forming the Coating

To fabricate the coating, the purified polymer, or a blend of purified polymers, can be applied on the stent using commonly used techniques known to those having ordinary skill in the art. For example, the polymer can be applied to the stent by dissolving the polymer in a coating solvent, or a mixture of solvents, and applying the resulting solution on the stent by spraying or immersing the stent in the solution.

Representative examples of some suitable coating solvents include N,N-dimethylacetamide (DMAC), N,N-dimethylformamide (DMF), tethrahydrofurane (THF), cyclohexanone, xylene, toluene, acetone, methyl ethyl ketone, propylene glycol monomethyl ether, methyl butyl ketone, ethyl acetate, n-butylacetate, and dioxane. Examples of suitable mixtures of solvents include mixtures of DMAC and methanol (e.g., a 50:50 by mass mixture), cyclohexanone and acetone (e.g., 80:20, 50:50, or 20:80 by mass mixtures), acetone and xylene (e.g., 50:50 by mass mixture), and acetone, FLUX REMOVER AMS, and xylene (e.g., 10:50:40 by mass mixture). FLUX REMOVER AMS is a trade name of a solvent manufactured by Tech Spray, Inc. of Amarillo, Tex. comprising about 93.7% of a mixture of 3,3-dichloro-1,1,1,2,2-pentafluoropropane, 1,3-dichloro-1,1,2,2,3-pentafluoropropane, and the balance methanol, with trace amounts of nitromethane.

In addition, blends of polymers can be used to fabricate the coating. In one embodiment, blends of polyacrylates, such as those listed in Table 1, can be used to fabricate the coating. In another embodiment, a blend of polyacrylates with non-acrylate materials is used. Poly(ethylene-co-vinyl alcohol) (EVAL) is one example of a suitable non-acrylate polymer. EVAL has the general formula —[CH_2—CH_2]$_q$—[CH_2—CH(OH)]$_r$—, where "q" and "r" are each an integer. EVAL may also include up to 5 molar % of units derived from styrene, propylene and other suitable unsaturated monomers. A brand of copolymer of ethylene and vinyl alcohol distributed commercially under the trade name EVAL by Aldrich Chemical Co., or manufactured by EVAL Company of America of Lisle, Ill., can be used.

Examples of other polymers with which polyacrylates can be blended include fluorinated polymers, such as poly(vinylidene fluoride) (PVDF) and poly(vinylidene fluoride-co-hexafluoro propene) (PVDF-HFP). The blend of a polyacrylate and a fluorinated polymer can contain between about 10 and about 95% (mass) of the fluorinated polymer.

Additionally, polymers other than polyacrylates can be used for the coating. Representative examples of suitable alternative polymers include EVAL, poly(hydroxyvalerate), poly(L-lactic acid), polycaprolactone, poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), polydioxanone, polyorthoester, polyanhydride, poly(glycolic acid), poly(D,L-lactic acid), poly(glycolic acid-co-trimethylene carbonate), polyphosphoester, polyphosphoester urethane; poly(amino acids), cyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), co-poly(ether-esters) (e.g. PEO/PLA), polyalkylene oxalates, polyphosphazenes, biomolecules (such as fibrin, fibrinogen, cellulose, starch, collagen and hyaluronic acid), polyurethanes, silicones, polyesters, polyolefins, polyisobutylene and ethylene-alphaolefin copolymers, acrylic polymers and copolymers other than polyacrylates, vinyl halide polymers and copolymers (such as polyvinyl chloride), polyvinyl ethers (such as polyvinyl methyl ether), polyvinylidene halides (such as polyvinylidene fluoride and polyvinylidene chloride), polyacrylonitrile, polyvinyl ketones, polyvinyl aromatics (such as polystyrene), polyvinyl esters (such as polyvinyl acetate), acrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers), polyamides (such as Nylon 66 and polycaprolactam), alkyd resins, polycarbonates, polyoxymethylenes, polyimides, polyethers, epoxy resins, polyurethanes, rayon, rayon-triacetate, cellulose, cellulose acetate, cellulose butyrate, cellulose acetate butyrate, cellophane, cellulose nitrate, cellulose propionate, cellulose ethers, and carboxymethyl cellulose.

The active agent or drug can include any substance capable of exerting a therapeutic or prophylactic effect for a patient. The drug may include small molecule drugs, peptides, proteins, oligonucleotides, and the like. The active agent could be selected, for example, to inhibit the activity of vascular smooth muscle cells. It can be directed at inhibiting abnormal or inappropriate migration and/or proliferation of smooth muscle cells to inhibit restenosis. Examples of drugs include immunosuppressive substances such as rapamycin and structural derivatives or functional analogs thereof, such as 40-O-(2-hydroxy)ethyl-rapamycin (known by the trade name of everolimus available from Novartis), 40-O-tetrazole-rapamycin, 40-O-(3-hydroxy)propyl-rapamycin and 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin; and antiproliferative substances such as actinomycin D, or derivatives and analogs thereof. Synonyms of actinomycin D include dactinomycin, actinomycin IV, actinomycin I_1, actinomycin X_1, and actinomycin C_1. The active agent can also fall under the genus of antineoplastic, anti-inflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antimitotic, antibiotic, antiallergic and antioxidant substances. Examples of such antineoplastics and/or antimitotics include paclitaxel, docetaxel, methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, doxorubicin, hydrochloride, and mitomycin. Examples of such antiplatelets, anticoagulants, antifibrin, and antithrombins include sodium heparin, low molecular weight heparins, heparinoids, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist antibody, recombinant hirudin, and thrombin. Examples of such cytostatic or antiproliferative agents include angiopeptin, angiotensin converting enzyme inhibitors such as captopril, cilazapril or lisinopril, calcium channel blockers (such as nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (ω-3-fatty acid), histamine antagonists, lovastatin (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug), monoclonal antibodies (such as those specific for Platelet-Derived Growth Factor (PDGF) receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitors, suramin, serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. An example of an antiallergic agent is permirolast potassium. Other therapeutic substances or agents which may be appropriate include alpha-interferon; genetically engineered epithelial cells; tacrolimus; and dexamethasone.

EXAMPLES

Some embodiments of the present invention are illustrated by the following Examples.

Example 1

About 15 grams of PBMA (medical grade, Lot PB 2375 from Esstech, Inc.) was combined with about 185 grams of HPLC grade methanol (available from Aldrich Chemical Co.). The mixture was stirred rigorously for 3 hours, and then the methanol was removed. This procedure was repeated for 5 cycles. After the last cycle, the polymer was vacuum dried at room temperature for about 24 hours to remove residual methanol.

Example 2

A sample of methanol from Example 1 that was removed after washing the polymer was studied to determine if impurities had been removed from the polymer. In particular, a Fourier Transform Infrared Spectrophotometer (available from Perkin-Elmer, Wellesley, Mass.) was used to compare the spectra from the removed methanol to the spectra of HPLC grade methanol (available from Aldrich Chemical Co.). Referring to FIG. **1**, the spectra for the PBMA wash had peaks at 1033 and 1053 cm−1. As shown in FIG. **2**, however, the spectra for the pure methanol had a peak at 1029 cm−1. FIG. **3** is an overlay of the two spectra, while FIG. **4** is a subtraction of the two spectra showing that there is a significant peak difference at 1029 cm−1. In short, FIG. **4** indicates that an impurity was washed from the polymer in Example 1.

Example 3

The purified polymer from Example 1 was dissolved in acetone (>99.5% purity, Class 10, Lot C01101, available from General Chemical Corporation, Detroit, Mich.) at 15% wt/wt. The solution was placed into a 50 ml centrifuge tube and run in a Model 225 Fisher Scientific Centrifuge (available from Fisher Scientific, Houston, Tex.). The centrifuge was set at a RPM setting of 6 and was run for about 30 minutes. The precipitate containing the impurities was collected and the solution was visually clean. The supernatant was then collected.

Example 4

The purified polymer (i.e., supernatant) from Example 3 was diluted to 2% PBMA in 80:20 acetone/cyclohexanone wt/wt to produce a coating composition. 3x13 mm TETRA stents (available from Guidant Corporation) were provided which are made of stainless steel. The stents were cleaned by sonicating for several minutes in de-ionized-water, methanol, then IPA. The stents underwent argon plasma treatment just before being coated.

Thirty-five 3x13 mm TETRA stents were coated with the purified polymer composition under the following conditions using a spray coater with an EFD 780S series nozzle: atomization pressure=about 8 psi; feeding pressure=about 3.95 psi; rotation speed=about 60 rpm; no translation motion; nozzle-to-stent distance=about 4.5 cm; spray time=about 2 sec; and waiting until next spray cycle=about 8 sec. After a number of spray cycles, the stents were dried at 70° C. for one hour to essentially remove the solvent and form a coating.

12 of the coated stents and 8 bare metal TETRA stents were then crimped onto a balloon catheter apparatus. The stents along with the balloon catheters were then sterilized by ETO for about 12 hours and then aerated for about 48 hours.

Example 5

9 of the coated stents and 5 of the bare metal stents from Example 4 were used to conduct an animal study. In particular, a 28 day porcine coronary artery model was used to determine if there was a significant biological response from the implantation of PBMA purified according to the methods of the present invention as compared to bare metal (i.e., stainless steel) stents. A standard implantation procedure was used to develop the histology data.

After the stented arteries were removed, they were processed using standard techniques to produce histology slides. Three sections of the stented vessels (i.e., proximal, media and distal) were used in the histology analysis. The percent stenosis was measured. The following Table 3 summarizes the histology data. The data is shown graphically in FIG. **5**, and FIG. **6** (bare metal stents) and 7 (PBMA coated stents) are sample histology photographs produced by the study.

TABLE 3

Bare Metal Stents	% Stenosis	Purified PBMA Coated Stents	% Stenosis
1	46.20	1	32.18
2	28.16	2	23.36
3	22.52	3	32.07
4	16.91	4	17.95
5	23.05	5	18.09
		6	26.61
		7	42.75
		8	24.64
		9	26.05
Average % Stenosis	27.37		27.08
Standard Deviation	11.26		7.76

As shown in the data of Table 3, and FIG. **5**, the area stenosis after 28 days as a result of an implantation of a stent with a purified polymer is substantially equivalent to the area stenosis after 28 days for a stent made of a biocompatible metal. Therefore, the purified polymer was shown to be biologically inert.

Example 6

PBMA (M_w=370K) is dissolved in acetone at 1 gram of PBMA per 5 grams of acetone (wt/wt). The polymer can be agitated or left at room temperature for a number of hours until the polymer become essentially dissolved in the solvent. Some of the low-density particles/aggregates (e.g., suspension agents) may become visible in the solution. The solution can then be exposed to vacuum filtration. The pore size of the filters can be from about 3 μm to about 10 μm.

Example 7

PBMA (M_w=370K) is dissolved in acetone at 1:7 (wt/wt). Drops of water/methanol (1:1 wt/wt) are slowly added into the solution while stirring until the rate of polymer precipitation decreases. The precipitated polymer is then recovered and vacuum-dried at 65° C. for 36 hours. The recovered polymer is then re-dissolved in xylene at 20% (wt/wt) for spray application.

Example 8

PBMA (M_w=370K) is dissolved in ethyl acetate at 15% wt/wt. The solution is placed in a Fisher Scientific Centrifuge, and the centrifuge is run for 30 minutes at a RPM setting of 6. The supernatant is collected. A portion of the supernatant is further diluted to 3% wt/wt and is transferred to a centrifugal filtration unit (available from Millipore). The centrifuge spin speed is set at 9.5 and the solution is centrifuged for about 4

hours. The process can be repeated. After about 24 hours of centrifugal filtration, a significant amount of the purified polymer can be collected.

Example 9

A polymer solution is prepared containing about 2.0 mass % of EVAL in DMAC. The solution is applied onto a stent to form a primer layer. To apply the primer layer, a spray apparatus such as the EFD 780S spray nozzle with a VALVEMATE 7040 control system, manufactured by EFD, Inc. of East Providence, Rhode Island is used. The EFD 780S spray nozzle is an air-assisted external mixing atomizer. The composition is atomized by air and applied to the stent surfaces. During the process of applying the composition, the stent is rotated about its longitudinal axis at a speed of about 100 rpm. The stent is also linearly moved along the same axis during the application.

The EVAL solution is applied to a 13-mm TETRA stent (available from Guidant Corporation) in a series of 10-second passes to deposit about 10 μg of coating per spray pass. Between the spray passes, the stent is dried for about 10 seconds using flowing air with a temperature of about 60° C. Five spray passes are, applied, followed by baking the primer layer at about 140° C. for one hour. As a result, a primer layer is formed having a solid content of about 50 μg. "Solid" means the amount of the dry residue deposited on the stent after essentially all volatile organic compounds (e.g., the solvent) have been removed.

A drug-containing formulation is prepared comprising:

(a) about 2.0 mass % of EVAL;

(b) about 1.0 mass % of everolimus; and

(c) the balance, a solvent mixture of DMAC and pentane, the solvent mixture containing about 80 (mass) % of DMAC and about 20 (mass) % of pentane.

In a manner identical to the application of the primer layer, five spray passes are performed, followed by baking the drug-polymer layer at about 50° C. for about 2 hours to form the drug-polymer layer having a solid content of about 90 μg and a drug content of about 30 μg.

Finally, a topcoat composition to control the drug release rate is prepared having purified PBMA. The PBMA polymer used for this example is first purified by solvent washing using methanol, and then centrifugal cleaning using acetone. The purified PBMA is then added to a solvent system and diluted to provide a 2.0 mass % solution, where the solvent system includes a 10:50:40 (mass) blend of acetone, Techspray's FLUX REMOVER AMS, and xylene. In a manner similar to the application of the primer layer and the drug-polymer layer, a number of spray passes are performed followed by final baking at about 50° C. for about 2 hours. As a result, a purified topcoat membrane is formed, the membrane having a solid content of about 50 μg.

Example 10

A primer layer is applied onto an 18-mm TETRA stent using PBMA purified by solvent washing using methanol followed by centrifugal cleaning using acetone. A drug formulation is prepared comprising:

(a) about 2.0 mass % of PBMA also purified by solvent washing using methanol followed by centrifugal cleaning using acetone;

(b) about 1.6 mass % of everolimus; and

(c) the balance, a solvent system having a 60:40 (mass) blend of acetone and xylene.

The drug formulation is applied onto the stent and a drug-polymer layer is formed in a manner similar to that described in Example 9. The solid content of the drug-polymer layer is about 1,000 μg. In this Example, the stent coating does not have a separate topcoat membrane.

Example 11

A primer layer is applied onto an 18-mm TETRA stent as described in Example 10. A drug formulation is then prepared including:

(a) about 2.0 mass % of P(MMA-BMA) having a weight-average molecular weight (M_w) of about 150,000 available from Aldrich Chemical Company. Before the P(MMA-BMA) polymer is added to the formulation, the polymer is purified by first washing with methanol and then extracting with soxhlet extraction using Techspray's FLUX REMOVER AMS for about 12 hours;

(b) about 1.0 mass % of everolimus; and

(c) the balance, a solvent system including a 10:50:40 (mass) blend of acetone, FLUX REMOVER AMS and xylene.

The P(MMA-BMA) contains about 79.2 mass % of units derived from BMA. The drug formulation is applied onto the dried primer layer in a manner similar to that described in Example 9, to form a drug polymer layer. The drug-polymer layer has the total amount of solid of about 520 μg. In this Example, the stent coating does not have a separate topcoat membrane.

Example 12

A primer layer and a drug-polymer layer are applied onto an 18-mm TETRA stent as described in Example 9. A blend of P(MMA-BMA) and PBMA is then purified by washing in methanol and then centrifugal cleaning with acetone as the solvent. A topcoat composition to control the drug release rate is prepared having about 2.0 mass % of a 1:1 (by mass) blend of purified P(MMA-BMA) and PBMA, and the balance solvent system. The solvent system includes a 10:50:40 (mass) blend of acetone, FLUX REMOVER AMS and xylene. The P(MMA-BMA)/PBMA blend can have about 83.3 mass % of units derived from BMA. The topcoat membrane is formed having a total amount of solid of about 30 μg.

Example 13

A primer layer is applied onto an 18-mm TETRA stent as described in Example 10. A drug formulation is then prepared including:

(a) about 2.0 mass % of PBMA-HEMA (n/m=7/3). Before the PBMA-HEMA polymer is added to the formulation, the polymer is purified by first washing with methanol and then centrifugal cleaning using acetone;

(b) about 1.6 mass % of everolimus; and

(c) the balance, a solvent system including a 70:30 (mass) blend of acetone and xylene.

The drug formulation is applied onto the dried primer layer to form the drug-polymer layer. The drug-polymer layer has a total amount of solid of about 600 μg. In this Example, the stent coating does not have a separate topcoat membrane.

Example 14

A primer layer and a drug-polymer layer are applied onto an 18-mm TETRA stent as described in Example 9. A select amount of PEMA is then purified by first washing with

methanol and then extracting with soxhlet extraction using FLUX REMOVER AMS for about 12 hours. A topcoat composition to control the drug release rate is prepared having about 2.0 mass % of purified PEMA, and the balance, a solvent system including a 80:20 (mass) blend of acetone and cyclohexanone. PEMA having a weight-average molecular weight M_w of about 101,400 available from Aldrich Chemical Company is one example of a brand of PEMA that can be used.

The topcoat composition is applied onto the dried drug-polymer layer. A number of spray passes are performed followed by final baking, at about 80° C. for about 1 hour. The topcoat membrane is formed having a solid content of about 40 μg.

While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications can be made without departing from this invention in its broader aspects. Therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of this invention.

What is claimed is:

1. A stent for implantation in a vessel of a patient, comprising a coating, the coating including a purified polymeric material which is completely or partially free from an impurity or impurities which cause the material to have a greater adverse biological response than the response caused by the material when the impurity or impurities have been removed or reduced from the material wherein the coating includes at least two layers, wherein at least one of the layers includes an active agent for the treatment of restenosis, wherein at least one of the layers includes the purified polymeric material, and wherein the purified polymeric material includes a polyacrylate material.

2. The stent of claim **1**, wherein the active agent is rapamycin, everolimus or derivatives or analogs of rapamycin or everolimus.

3. The stent of claim **1**, wherein the polymeric material prior to purification is a medical grade polymer as sold by the manufacturer.

4. The stent of claim **1**, wherein the polymeric material is purified by a process selected from the group consisting of solvent washing, centrifugal cleaning, soxhlet extraction, filtration, step precipitation, centrifugal filtration or a combination thereof.

5. The stent of claim **1**, wherein the purified polymeric material has generally the same degree of biological inertness as stainless steel.

6. A stent for implantation in a vessel of a patient, comprising a coating, the coating including a purified polymeric material which is completely or partially free from an impurity or impurities which cause the material to have a greater adverse biological response than the response caused by the material when the impurity or impurities have been removed or reduced from the material, wherein the polymeric material includes poly(butyl methacrylate) and the coating additionally comprises rapamycin or functional analog or structural derivative thereof.

7. The stent of claim **6**, wherein the coating includes at least two layers, wherein the outer most layer of the coating is made from the purified polymeric material.

8. The stent of claim **6**, wherein the polymeric material is a blend of at least two polymers.

9. The stent of claim **6**, wherein the polymeric material prior to purification is a medical grade polymer as sold by the manufacturer.

10. The stent of claim **6**, wherein the polymeric material is purified by a process selected from the group consisting of solvent washing, centrifugal cleaning, soxhlet extraction, filtration, step precipitation, centrifugal filtration or a combination thereof.

11. The stent of claim **6**, wherein the purified polymeric material has generally the same degree of biological inertness as stainless steel.

12. A stent used for implantation in a vessel of a patient, comprising a coating, the coating including a purified medical grade polymeric material which is completely or partially free from an impurity or impurities which cause the material to have a greater adverse biological response than the response caused by the material when the impurity or impurities have been removed or reduced from the material.

13. The stent of claim **12**, wherein the polymeric material is selected from a group consisting of poly(n-butyl methacrylate), poly(iso-butyl methacrylate), poly(tert-butyl methacrylate), poly(methyl methacrylate), poly(ethyl methacrylate), poly(n-propyl methacrylate), poly(methyl acrylate), poly(n-hexyl methacrylate), poly(methyl methacrylate-co-n-butyl methacrylate), poly(n-butyl methacrylate-co-iso-butyl methacrylate), poly(n-butyl methacrylate-co-2-hydroxyethyl methacrylate), poly(methyl methacrylate-co-2-hydroxyethyl methacrylate) and poly(ethyl methacrylate-co-2-hydroxyethyl methacylate).

14. The stent of claim **12**, wherein the polymeric material is a polyacrylate material.

15. The stent of claim **12**, wherein the coating includes at least two layers, wherein the outer most layer of the coating is made from the purified polymeric material.

16. The stent of claim **12**, wherein the coating includes at least two layers, wherein at least one of the layers includes an active agent for the treatment of restenosis, wherein at least one of the layers is made from the purified polymeric material, and wherein the purified polymeric material includes a polyacrylate material.

17. The stent of claim **12**, wherein the polymeric material includes poly(butyl methacrylate) and the coating additionally comprises rapamycin.

18. The stent of claim **12**, wherein the coating additionally comprises an active agent.

19. The stent of claim **18**, wherein the active agent is rapamycin, everolimus or derivatives or analogs of rapamycin or everolimus.

20. The stent of claim **12**, wherein the polymeric material is a blend of at least two polymers.

21. The stent of claim **12**, wherein the purified polymeric material has generally the same degree of biological inertness as stainless steel.

22. The stent of claim **12**, wherein the polymeric material is a medical degrade polymer that is not purified as supplied by the manufacturer and prior to being coated on the stent.

23. A stent comprising a coating, the coating including a purified version of a medical grade polymeric material that has generally the same degree of biological inertness as stainless steel when implanted in a blood vessel of a mammal.

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